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The Effect of Organic Salts on HPMC

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Abstract

The presence of organic salts as drug counter-ions and buffers in hydroxypropylmethylcellulose (HPMC) matrices is often overlooked. This study investigates their potential to influence polymer solution properties and matrix drug release kinetics.

A homologous series of aliphatic organic salts influenced solution and matrix properties in rank order of hydrocarbon chain length. Monovalent salts containing 1 to 4 C-atoms had little effect on polymer surface activity, but lowered sol:gel transition temperatures (SGTT), and accelerated matrix drug release in comparison with a dextrose control. Divalent salts were more potent. These observations are consistent with Hofmeister effects in which anions restructure water in the polymer hydration sheath, induce 'salting-out' and suppressing particle swelling and matrix gel layer formation. Organic salts with 5 to 8 C-atoms increasingly influenced polymer surface activity, elevated SGTT, and retarded matrix drug release. This suggests these salts enhance HPMC hydration, possibly through interaction with hydrophobic regions. The effects of these salts on matrix drug release show that these ions impact on water:polymer interactions important to gel layer formation and diffusion barrier properties. HPMC matrices containing SDS and its homologues were also investigated. Turbidimetric, tensiometric and rheological studies supported a mechanism in which these surfactants solubilise HPMC at post-micellar concentrations. Incorporating 10% SDS into HPMC matrices was shown to increase the resistance of HPMC matrices to sucrose medium up to 2.0M, suggesting a role for surfactants in avoiding food solute effects

This study shows that organic salts incorporated in HPMC matrices have the potential to influence drug release in a rank order that reflects their modulation of the HPMC polymer hydration sheath in solution. SDS and its homologous series could retard drug release from HPMC matrices only when their critical aggregation concentration (CAC) was reached. However, it suggests this excipient may have uses as an excipient for improving HPMC matrix release performance.

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Table of contents

Abstract.....	i
Acknowledgements.....	ii
Table of contents.....	iv
List of figures.....	xii
List of tables.....	xviii
List of symbols and abbreviations	xxi

Chapter 1: Introduction

1.1 Cellulose ethers and derivatives.....	2
1.2 Hydroxypropylmethylcellulose (HPMC).....	3
1.2.1 HPMC Types and applications	4
1.3 The properties of HPMC solutions	6
1.3.1 Thermal gelation.....	6
1.3.1.1 Mechanism of thermal gelation	6
1.3.1.2 Factors affecting the sol:gel transition of cellulose ethers.....	9
1.3.2 Rheology.....	11
1.3.3 Surface activity.....	12
1.4 The properties of HPMC matrices.....	13
1.4.1 Hydrophilic matrices.....	13
1.4.2 Mechanism of drug release.....	13
1.4.3 A mathematical model for determining the drug release mechanism from HPMC matrices.....	16
1.4.4 Factors affecting matrix drug release.....	18
1.4.4.1 Polymer factors.....	18
1.4.4.2 Non-polymer factors.....	22

1.5 Organic salts	28
1.5.1 The applications of organic salts.....	28
1.5.1.1 Organic salts used as drugs.....	28
1.5.1.2 Organic salts used as drug counter-ions.....	28
1.5.1.2.1 A survey of the use of organic salts as counter-ions to drugs	29
1.5.2 Hofmeister effect	37
1.6 Surfactants.....	39
1.6.1 The Solution Properties of Surfactants	39
1.6.2 Surfactant-Polymer Systems.....	42
1.6.3 Surfactants in Pharmaceutical applications.....	44
1.7 Thesis aims and objectives.....	48
1.7.1 Principal aims.....	48

Chapter 2: Materials and General Methods

2.1 Materials.....	50
2.1.1 Hydroxypropyl methylcellulose (HPMC).....	50
2.1.2 Other materials.....	50
2.2 Methods.....	51
2.2.1 The preparation of HPMC solutions.....	51
2.2.1.1 10% w/w HPMC stock solutions.....	51
2.2.1.2 1-2% w/w HPMC stock solutions.....	51
2.2.2 The preparation of 0.1% and 1% w/w HPMC solutions containing additives.....	51
2.2.3 Turbidimetric determination of HPMC cloud point temperature.....	52
2.2.3.1 Operational method.....	52
	54

2.2.4	Tensiometric determinations of HPMC surface tension.....	54
2.2.4.1	Measuring surface tension using a profile analysis tensiometer.....	55
2.2.4.2	Surface tension measurements of HPMC solutions.....	55
2.2.5	Density measurement.....	56
2.2.6	Rheological determinations.....	56
2.2.6.1	Rheology, viscosimetry and viscoelasticity.....	58
2.2.6.2	Dynamic oscillatory rheology.....	60
2.2.6.3	Descriptive factors used in oscillatory rheology.....	61
2.2.6.4	Operational method.....	63
2.2.7	The manufacture of HPMC hydrophilic matrix tablets.....	63
2.2.7.1	The preparation of formulation blends.....	63
2.2.7.2	The manufacture of matrix tablets.....	63
2.2.7.3	The labelling and storage of matrix tablets.....	64
2.2.8	Dissolution testing of matrix tablets.....	
2.2.8.1	Mathematical models for determining the drug release mechanism of HPMC matrices.....	64
2.2.9	Confocal laser scanning microscopy (CLSM).....	67
2.2.9.1	Theory of CLSM.....	69
2.2.9.2	Congo red.....	71
2.2.9.3	Operational method.....	73
2.2.10	Routine monitoring of HPMC powder moisture content.....	

Chapter 3: The Effect of Organic Salts on HPMC Solutions

3.1	Rationale.....	74
3.2	Introduction.....	74
3.2.1	Previous studies of additives affecting the properties of HPMC solutions	74
3.2.2	The studies of organic acids and salts with HPMC	75

3.3 Chapter aims and objectives	76
3.4 Materials and methods	77
3.4.1 Organic salts	77
3.4.1.1 Homologous series	77
3.4.1.2 Structure activity relationships	77
3.4.2 HPMC	81
3.4.3 Manufacture of HPMC solutions	81
3.4.4 Turbidimetric determinations	82
3.4.5 Surface tension measurements	82
3.4.6 Density measurements	82
3.4.7 Rheological determinations	82
3.4.7.1 Amplitude sweeps	83
3.4.7.2 Frequency sweeps	83
3.4.7.3 Temperature sweeps	84
3.5 Results and discussion.....	85
3.5.1 The effect of organic salts on the sol-gel transition temperature (SGTT) of HPMC solutions.....	85
3.5.1.1 Homologous series of salts	85
3.5.1.2 Structure activity relationships	89
3.5.1.3 The effect of functional groups and anion structure	93
3.5.2 The effect of organic salts on the surface tension of HPMC solutions	97
3.5.3 The effect of organic salts on the viscoelastic properties of HPMC solutions...	102
3.5.3.1 Homologous series	102
3.5.3.2 Structure activity relationships	109
3.5.4 The interaction between organic salts and HPMC	129
3.6 Conclusions.....	133

Chapter 4: The Effect of Organic Salts on HPMC Matrices

4.1 Rationale	135
4.2 Introduction.....	135
4.3 Chapter aims and objectives.....	137
4.4 Materials and methods.....	138
4.5.1 Organic salts.....	138
4.5.1.1 A homologous series.....	138
4.5.1.2 The relative groups....	138
4.5.2 HPMC.....	138
4.5.3 Manufacture of matrix tablets.....	138
4.5.4 Dissolution determination.....	142
4.5.4.1 The preparation of dissolution media.....	142
4.5.5 Statistical analysis.....	142
4.5.6 Photography of hydrating HPMC matrices.....	143
4.5 Results and discussion.....	144
4.5.1 The selection of the dissolution media.....	144
4.5.2 The effect of 60% organic salts on drug release from HPMC matrices.....	147
4.5.2.1 The effect of the C-chain length of organic salts on drug release from HPMC matrices (homologous series).....	149
4.5.2.2 The effect of the structure relationship of organic salts on drug release from HPMC matrices.....	151
4.5.3 The influence of diluents on the effect of organic salts on drug release.....	163
4.5.3.1 The effect of diluents on drug release from HPMC matrices.....	163
4.5.3.2 The effect of diluents on drug release from HPMC matrices containing disodium succinate.....	169
4.5.3.3 The effect of 10% organic salt on drug release from HPMC matrices containing diluents.....	177

4.5.4 A correlation between the effects of organic salts on HPMC matrix drug release, and their effect on the thermogelation temperature (SGTT) of HPMC solutions.....	188
4.6 Conclusions.....	192

Chapter 5: The Effect of Alkyl Sulphate Surfactants on HPMC Solutions and HPMC Matrices

5.1 Rationale	195
5.2 Introduction.....	195
5.2.1 Alkyl Sulphate Surfactants	195
5.2.2 Surfactants and Cellulose Ethers.....	197
5.3 Chapter aims and objectives.....	199
5.4 Materials and methods.....	200
5.4.1 Surfactants	200
5.4.2 HPMC.....	201
5.4.3 Manufacture of HPMC solutions.....	201
5.4.4 Turbidimetric determination.....	202
5.4.5 Surface tension measurement.....	202
5.4.6 Density measurement.....	202
5.4.7 Manufacture of matrix tablets.....	203
5.4.8 Compression force-hardness profiles.....	203
5.4.9 Dissolution determination.....	203
5.4.10 Investigation of the early gel layer formation by confocal laser scanning microscopy.....	205
5.5 Results and discussion.....	206
5.5.1 The effect of surfactants on HPMC solutions	206
5.5.1.1 The effect of surfactants on the surface tension of HPMC solutions.....	206

5.5.1.2	The effect of surfactants on the density of HPMC solutions	210
5.5.1.3	The effect of surfactants on the sol:gel transition temperature (SGTT) of HPMC solutions.....	212
5.5.1.4	The effect of surfactants on the rheological properties of HPMC solutions.....	215
5.5.2	The mechanism of interaction between surfactants and HPMC in solution....	218
5.5.3	The effect of surfactants on HPMC matrices	221
5.5.3.1	Compression pressure – hardness profile of HPMC matrix tablets	221
5.5.3.2	The effect of surfactant content on the matrix drug release profile	223
5.5.3.3	The effect of tablet diluents on drug release from HPMC matrices containing surfactants.....	227
5.5.3.4	The early gel layer development of HPMC matrices containing SDS.....	233
5.5.4	The effect of alkyl chain length of surfactants on HPMC	235
5.6	Conclusions.....	239

Chapter 6: The Recovery of HPMC Matrices using SDS

6.1	Rationale.....	240
6.2	Introduction	240
6.2.1	The previous studies of SDS and HPMC.....	240
6.2.2	Previous studies of the failing HPMC matrix formulations and under challenging conditions.....	241
6.3	Chapter aims and objectives	244
6.4	Materials and Methods	245
6.4.1	HPMC matrix tablet.....	245
6.4.2	Failing formulations.....	245
6.4.3	Challenging conditions.....	245
6.4.4	Manufacture of matrix tablets.....	245

6.4.5	Dissolution testing.....	247
6.4.6	Photography of hydrating HPMC matrix tablets.....	247
6.5	Results and discussions.....	248
6.5.1	Does SDS enhance the extended release properties of the ‘failing formulation’?	248
6.5.2	Does SDS enhance the extended release properties of HPMC matrices under challenging conditions?	250
6.5.2.1	The effect of incorporating SDS on the extended release performance of HPMC matrices in sucrose media.....	250
6.5.2.2	The effect of SDS on the appearance of HPMC matrices in sucrose media.....	257
6.6	Conclusions.....	263

Chapter 7: Overall Discussion and conclusions

7.1	Overall discussion.....	264
7.1.1	Organic salts.....	264
7.1.2	Alkyl sulphate surfactants.....	267
7.2	Overall conclusions	270
7.3	Future work.....	272
References		273

Appendices

Materials.....	A1
The moisture content of the principal HPMC batch monitored over the duration of work in this thesis.....	A3
The effect of compression force on HPMC matrices using dextrose as a diluent.....	A4
Presentations.....	A5

List of figures

Chapter 1:

Figure 1.1	HPMC structure.....	3
Figure 1.2	The substitution ranges of commercial Methocel™ HPMC grades.....	5
Figure 1.3	Schematic illustration of the postulated structures and processes involved in the thermal gelation of MC (HPMC A4M).....	8
Figure 1.4	The principal drug release mechanism of a hydrophilic matrix tablet.....	15
Figure 1.5	Schematic illustration of a cross-section HPMC matrix tablet during hydration and drug release.....	15
Figure 1.6	Generalised structure of a surfactant micelle in water.....	41
Figure 1.7	Schematic representation of the concentration dependence of some physical properties for solutions of micelle-forming surfactants.....	41
Figure 1.8	Schematic plot of the surface tension of surfactant solutions as a function of surfactant concentration in the presence of polymer.....	43

Chapter 2:

Figure 2.1:	Schematic diagram of the cloud point temperature apparatus.....	53
Figure 2.2:	(a) a pendant drop of liquid.....	
	(b) the liquid meniscus used for the Gauss-Laplace calculation.....	55
Figure 2.3:	Schematic diagram of a single Maxwell model illustrating the deformation of a viscoelastic sample on application of a force.....	57
Figure 2.4:	Schematic stress response to oscillatory strain deformation for (a) a purely elastic solid, (b) a purely viscous liquid and (c) a viscoelastic material.....	59
Figure 2.5:	Schematic diagram illustrating the parallel plate (PP 2°/50mm) geometry used for rheological determinations of HPMC solutions.....	62
Figure 2.6:	Dynamic amplitude sweep on a 2%w/w HPMC solution with respect to storage modulus (G') and loss modulus (G'').....	62
Figure 2.7:	Schematic diagram of the principal elements and light paths within a confocal laser scanning microscope.....	68
Figure 2.8:	The chemical structure of Congo red.	70
Figure 2.9:	Schematic diagram of the experimental geometry used during confocal imaging, "Fixed Observational Geometry" (FOG).....	72

Chapter 3:

Figure 3.1:	Effect of the homologous series of salts on SGTT of HPMC E4M.....	87
Figure 3.2:	Effect of the homologous series of salts on SGTT of HPMC K4M.....	88
Figure 3.3:	Effect of the organic salts on SGTT of HPMC E4M.....	91
Figure 3.4:	The effect of the number of carboxyl groups of the organic salts on the sol-gel transition temperature (SGTT) of 1%w/w HPMC E4M solution.....	95
Figure 3.5:	The effect of organic salts containing 4 C-atoms on the sol-gel transition temperature (SGTT) of 1%w/w HPMC E4M solution.....	95
Figure 3.6:	A comparison of carboxylate and sulphonate organic salts on the sol-gel transition temperature (SGTT) of 1%w/w HPMC E4M solution.....	96
Figure 3.7:	The effect of hydroxyl group substituents on organic salt molecules on the sol-gel transition temperature (SGTT) of 1%w/w HPMC E4M solution.....	96
Figure 3.8:	Low surface activity group - The effect of organic salt concentration on the surface tension of water and 0.1% w/w HPMC E4M solution at 20°C (a) sodium acetate (b) sodium propionate (c) sodium butyrate.....	99
Figure 3.9:	Surface active group - The effect of organic salt concentration on the surface tension of water and 0.1% w/w HPMC E4M solution at 20°C (a) sodium pentanoate (b) sodium caproate (c) disodium tartrate (d) sodium octanoate.....	100
Figure 3.10:	Aromatic group - The effect of organic salt concentration on the surface tension of water and 0.1% w/w HPMC E4M solution at 20°C (a) sodium benzoate (b) sodium besilate (c) sodium salicylate.....	101
Figure 3.11:	Frequency dependence of (a) complex viscosity (b) elastic modulus, G' (c) viscous modulus, G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions containing the initial homologous series of organic salts.....	106
Figure 3.12:	Temperature dependence of G' and G'' for 2% w/w HPMC solutions containing the initial homologous series of organic salts.....	108
Figure 3.13:	The effect of geometric isomerism of the organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions.	112
Figure 3.14:	The effect of ionisation of fumarate salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ in 2% w/w HPMC solutions.....	116
Figure 3.15:	A comparison of carboxylate and sulfonate organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions.....	120

Figure 3.16:	The effect of the presence of hydroxyl group(s) within the organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions.....	125
Figure 3.17:	The effect of number of carboxyl groups within the organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions.....	129
Figure 3.18:	Illustration of the postulated mechanisms between HPMC and organic salts containing (a) 1-4 C-atoms (b) over 6 C-atoms and (c) containing an aromatic ring.....	133

Chapter 4:

Figure 4.1:	The effect of dissolution media on the drug release profile of HPMC matrices containing sodium acetate, sodium pentanoate or sodium octanoate. Dissolution media are (a) water (b) 0.15M NaCl (c) 0.15M KCl and (d) SGF without enzyme.....	146
Figure 4.2:	The effect of C-chain length of the organic salts on the drug release profile of HPMC matrices.....	150
Figure 4.3:	The effect of fumarate/maleate geometric isomerism of the organic salts on the drug release profile of HPMC matrices.....	152
Figure 4.4	The effect of ionisation of fumarate salts on the drug release profile of HPMC matrices.....	154
Figure 4.5:	The intermolecular π - π and sulfur-sulfur interactions between adjacent molecules.....	156
Figure 4.6:	A comparison of carboxylate and sulfonate organic salts on the drug release profile of HPMC matrices.....	157
Figure 4.7:	The orientation of tartrate structure in (a) solution (b) solid.....	159
Figure 4.8:	The effect of hydroxyl group substituents on the release profile of HPMC matrices.	160
Figure 4.9:	The effect of number of carboxyl groups within the organic salts on the release profile of HPMC matrices.....	162
Figure 4.10:	Compression pressure – hardness profile for HPMC matrix tablets containing the different diluents.....	167
Figure 4.11:	The effect of partially pregelatinised starch (Starch1500) on the dissolution profile of HPMC matrices (E4M, E4M (63-90 μ m fraction), and K4M).	167
Figure 4.12:	The effect of MCC on the dissolution profile of HPMC matrices (E4M, E4M (63-90 μ m fraction), and K4M).....	168
Figure 4.13:	The effect of Dextrose on the dissolution profile of HPMC matrices (E4M, E4M (63-90 μ m fraction), and K4M).....	168

Figure 4.14:	The effect of partially pregelatinised starch (Starch1500) on the dissolution profile of HPMC matrices containing disodium succinate which (a) E4M (b) E4M (63-90 μ m fraction) and (c) K4M.....	173
Figure 4.15:	The effect of MCC on the dissolution profile of HPMC matrices containing disodium succinate which (a) E4M (b) E4M (63-90 μ m fraction) and (c) K4M..	174
Figure 4.16:	The effect of dextrose on the dissolution profile of HPMC matrices containing disodium succinate which (a) E4M (b) E4M (63-90 μ m fraction) and (c) K4M.....	175
Figure 4.17:	The difference of using native and sieved HPMC E4M on the drug release profile of HPMC matrices.....	176
Figure 4.18:	The difference of using native and sieved HPMC E4M on the drug release profile of HPMC matrices containing disodium succinate.....	176
Figure 4.19:	The effect of C-chain length of 10% w/w organic salts on the drug release profile of HPMC matrices.....	180
Figure 4.20:	(a) The microscopic photographs of HPMC matrix tablets containing 10% sodium octanoate taken from USP dissolution baskets at at different times during the dissolution test.....	180
	(b) The photograph of HPMC matrix tablets containing 10% sodium octanoate taken from USP dissolution baskets at at different times during the dissolution test.....	180
Figure 4.21:	The effect of fumarate/maleate geometric isomerism (10%w/w) on the drug release profile of HPMC matrices.....	182
Figure 4.22:	The effect of ionisation of fumarate salts (10%w/w) on the drug release profile of HPMC matrices.....	182
Figure 4.23:	A comparison of carboxylate and sulphonate organic salts (10%w/w) on the drug release profile of HPMC matrices.....	184
Figure 4.24:	A comparison of 10%w/w and 60%w/w carboxylate and sulfonate organic salts on the drug release profile of HPMC matrices.....	184
Figure 4.25:	The effect of hydroxyl group substituents on the release profile of HPMC matrices (10%w/w salt)	187
Figure 4.26:	The effect of the number of carboxyl groups on the release profile of HPMC matrices (10%w/w salt)	187
Figure 4.27:	Correlation between the effect of (a) 10%w/w (b) 60%w/w organic salts on the sol:gel transition temperature (SGTT) of HPMC solutions and on the time to 80% cumulative drug release ($T_{80\%}$) of HPMC matrices.....	190
Figure 4.28:	Correlation between the effect of (a) 10%w/w (b) 60%w/w organic salts on the sol:gel transition temperature (SGTT) of HPMC solutions and on the release rate (k) of HPMC matrices.....	191

Chapter 5:

Figure 5.1:	General structure of an alkyl sulphate surfactant.....	196
Figure 5.2:	The effect of HPMC concentration on the surface tension of water at 20°C.....	207
Figure 5.3:	The effect of alkyl sulphate surfactant concentration on the surface tension of water and 0.1% w/w HPMC E4M CR solution at 20°C (a) SHS (b) SOS (c) SDeS (d) SDS.....	208
Figure 5.4:	The effect of surfactant concentration on the density of (a) water, (b) 0.1%w/w HPMC solutions in the presence of a homologous series of alkyl sulphate surfactants.....	211
Figure 5.5:	The effect of SDS concentration on the cloud point of 1%w/w HPMC E4M solutions.....	213
Figure 5.6:	The effect of the concentration of a homologous series of alkyl sulphate surfactants on 1%w/w HPMC E4M solution.....	213
Figure 5.7:	The ability of a homologous series of alkyl sulphate surfactants to elevate CPT of 1%w/w HPMC E4M solution at the post-micellar phase.....	214
Figure 5.8:	The effect of SDS concentration on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2%w/w HPMC solutions.	216
Figure 5.9:	Illustration of the mechanism between HPMC and surfactants.....	220
Figure 5.10:	Illustration of the postulated mechanism between HPMC and surfactants – larger surfactant.....	220
Figure 5.11:	Compression pressure - hardness profiles for HPMC matrix tablets containing the different amounts of SDS.....	222
Figure 5.12:	Compression pressure - hardness profiles for HPMC matrix tablets containing 10%w/w of different alkyl sulphate surfactants.....	222
Figure 5.13:	The effect of surfactant content (a) SOS, (b) SDeS or (c) SDS on drug release from HPMC matrices.....	225
Figure 5.14:	The effect of surfactant content on T80% drug release.....	226
Figure 5.15:	The effect of a homologous series of alkyl sulphate surfactants on the drug release profile of HPMC matrices containing (a) dextrose, (b) Starch1500, (c) dextrose: Starch1500 (1:1), (d) MCC or (e) dextrose:MCC (1:1) as diluents.....	229
Figure 5.16:	The effect of replacing Dextrose with (a) Starch1500 or (b) MCC on the drug release profile of HPMC matrices containing surfactants.....	232
Figure 5.17:	Early gel layer formation at the boundary of hydrating HPMC matrices (a) 0%w/w SDS (b) 10%w/w SDS. Matrices contained dextrose as a diluent.....	234

Figure 5.18:	The correlation between the ability of surfactants to elevate SGTT of 1%w/w HPMC solution and their alkyl chain length.....	237
Figure 5.19:	The correlation between the CAC of surfactants in a 0.1%w/w HPMC solution and their alkyl chain length.....	238
Figure 5.20:	The effect of alkyl chain length of surfactants on drug release from HPMC matrix tablets containing different diluents.....	238

Chapter 6:

Figure 6.1:	'Failing formulations' study: The effect of SDS on the release profile of HPMC matrices containing sodium acetate.....	249
Figure 6.2:	'Failing formulations' study: The effect of SDS on the release profile of HPMC matrices containing disodium succinate.....	249
Figure 6.3:	'Challenging conditions' study: The drug release performance of HPMC matrices without SDS (control) in a range of sucrose dissolution media.....	253
Figure 6.4:	'Challenging conditions' study: The effect of incorporating 1%w/w SDS on the drug release profile of HPMC matrices in different sucrose media...	254
Figure 6.5:	'Challenging conditions' study: The effect of incorporating 5%w/w SDS on the drug release profile of HPMC matrices in different sucrose media...	255
Figure 6.6:	'Challenging conditions' study: The effect of incorporating 10%w/w SDS on the drug release profile of HPMC matrices in different sucrose media...	256
Figure 6.7:	'Challenging conditions' study: The photographs of HPMC matrix tablets containing 10% SDS taken from USP dissolution baskets at at different times during the dissolution test.....	260
Figure 6.8:	The microscopic photographs of HPMC matrix tablets containing 10% SDS taken from USP dissolution baskets at at different times during the dissolution test.....	261
Figure 6.9:	The photograph of the gel mass left in the end of the dissolution test taken from USP dissolution baskets at 8 hours.....	261

List of tables

Chapter 1:

Table 1.1:	Substitution levels and important physical properties of different HPMC types.....	5
Table 1.2:	The category of drug transport from the controlled release matrices classified by the diffusional exponent (n).....	17
Table 1.3:	Organic species currently used as drug counter-ions.....	30
Table 1.4:	Surfactants commonly used in Pharmaceutical applications.....	45

Chapter 2:

Table 2.1:	The results of fitting drug release data to some mathematical models.....	66
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Chapter 3:

Table 3.1:	The homologous series of 1-carboxyl aliphatic salts used in this chapter.....	78
Table 3.2:	Organic salts used in the study of structure activity relationships in this chapter.....	79
Table 3.3:	Organic salts: The linear correlation (r) and slope (Δ CPT) of curve between aliphatic salts concentration and cloud point temperature (CPT)...	86
Table 3.4:	The linear correlation (r) and slope (Δ CPT) of curve between aliphatic salts concentration and cloud point temperature (CPT).....	92
Table 3.5:	Rheological data of HPMC solutions (2%w/w) containing the initial homologous series of organic salts.....	105
Table 3.6:	Rheological data of HPMC solutions (2%w/w) containing organic salts: the effect of geometric isomerism.....	111
Table 3.7:	Rheological data of HPMC solutions (2%w/w) containing fumarate salts: the effect of ionization.....	115
Table 3.8:	Rheological data of HPMC solutions (2%w/w) containing organic salts: A comparison of carboxylate and sulfonate organic salts.....	119
Table 3.9:	Rheological data of HPMC solutions (2%w/w) containing organic salts: the effect of the hydroxyl group substituents.....	124
Table 3.10:	Rheological data of HPMC solutions (2%w/w) containing organic salts: the effect of number of carboxyl groups.....	128

Chapter 4:

Table 4.1:	The formulation of HPMC matrix tablets containing (A) high amount salts (B) low amount salts used in this chapter.....	140
Table 4.2:	The formulation of HPMC matrix tablets used in the study of the effect of diluents on HPMC matrices.....	140
Table 4.3:	The formulation of HPMC matrix tablets used in the study of the effect of diluents on HPMC matrices containing disodium succinate.....	141
Table 4.4:	The difference factor (f_1) and the similarity factor (f_2) between HPMC matrices containing acetate Na and pentanoate Na.....	144
Table 4.5:	The effect of 60% organic salts on drug release kinetics using the modified power law.....	148
Table 4.6:	The effect of an aliphatic homologous series of organic salts on drug release kinetics using the modified power law and linear regression.....	150
Table 4.7:	The effect of fumarate/maleate geometric isomerism of the organic salts on drug release kinetics using the modified power law and linear regression.....	152
Table 4.8:	The effect of ionisation of fumarate salts on drug release kinetics using the modified power law and linear regression.....	154
Table 4.9:	A comparison of carboxylate and sulfonate organic salts on drug release kinetics using the modified power law and linear regression.....	157
Table 4.10:	The effect of hydroxyl group substituents on drug release kinetics using the modified power law and linear regression.....	160
Table 4.11:	The effect of number of carboxyl groups within the organic salts on drug release kinetics using the modified power law and linear regression.....	162
Table 4.12:	The effect of diluents on drug release kinetics using the modified power law.....	166
Table 4.13:	The effect of diluents on drug release kinetics of HPMC matrices containing disodium succinate using the modified power law.....	172
Table 4.14:	The effect of 10% organic salts on drug release kinetics in the presence of diluents using the modified power law.....	178

Chapter 5:

Table 5.1:	The homologous series of alkyl sulphate surfactants used in this chapter.....	200
Table 5.2:	The formulation of HPMC matrix tablets used in this chapter.....	204
Table 5.3:	cmc and CAC values for a homologous series of alkyl sulphate surfactants in 0.1%w/w HPMC solution.....	207
Table 5.4:	The effect of surfactant content on drug release kinetics using the modified power law.....	224
Table 5.5:	The effect of diluents on drug release kinetics of HPMC matrices containing surfactants using the modified power law.....	228

Table 5.6:	Dependence of HPMC solution and matrix drug release properties on alkylsulphate chain length.....	237
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Chapter 6:

Table 6.1:	The formulation of HPMC matrix tablets used in the 'failing matrices' studies.....	246
Table 6.2:	The formulation of HPMC matrix tablets used in the 'challenging conditions' studies.....	246
Table 6.3:	'Challenging conditions studies: The effect of incorporated SDS into HPMC matrices on drug release kinetics in different sucrose concentration using the modified power law.....	252
Table 6.4:	'Challenging conditions' study: The observed appearance of HPMC matrix tablets with 0%, 1%, 5%, and 10% SDS during dissolution tests in different sucrose media.....	259
Table 6.5:	'Challenging conditions' study: The capacity of SDS to recover HPMC matrices (with Dextrose as a diluent) in sucrose dissolution media.....	262

List of symbols and abbreviations

c	Spring constant
CAC	Critical aggregation concentration
CLSM	Confocal laser scanning microscopy
cmc	Critical micelle concentration
CPT	Cloud point temperature
f	Frequency (Hz)
F	Force
g	Acceleration due to gravity
G'	Elastic or storage modulus
G''	Viscous or loss modulus
h	Height
HM-HEC	Hydrophobically modified hydroxyethyl cellulose
HPMC	Hydroxypropyl methylcellulose
HPMC E4M	Hydroxypropyl methylcellulose USP Type 2910 (Methocel™ E4M CR Premium EP/USP)
HPMC K4M	Hydroxypropyl methylcellulose USP Type 2208 (Methocel™ K4M CR Premium EP/USP)
Hz	Hertz (unit of frequency)
k, k₁, k₂	Kinetic constants
KCl	Potassium chloride
l	Lag time
LVR	Linear viscoelastic range
M	Cell mass
m	Diffusional exponent for drug release
M_t	The amount of drug released at time t
M_∞	The amount of drug released at infinite time
MC	Methylcellulose
mg	Milligram
mL	Millilitre

mm	Millimetre
MPa	Megapascal
n	Number of samples
n	Diffusional exponent for drug release
NaCl	Sodium chloride
ΔP_0	Pressure difference in a reference plane,
Pa	Pascal
PMT	Photo multiplier tube
PP	Parallel-plate
(geometry)	
PVP	Poly(vinylpyrrolidone)
r^2	Coefficient of determination
R_1, R_2	The main radii of curvature
SDS	Sodium dodecyl sulphate
SDeS	Sodium decyl sulphate
SGF	Simulated gastric fluid
SGTT	Sol:gel transition temperature
SHS	Sodium hexyl sulphate
SOS	Sodium octyl sulphate
t	Time
$T_{80\%}$	Time taken to achieve 80% cumulative drug release
T_g	Thermal glass transition
Tan δ	Loss or damping factor
USP	The United States Pharmacopeia
UV	Ultraviolet
v	Cell volume
$^{\circ}\text{C}$	Degree Celsius
% w/v	Percentage
γ	Surface tension (tensiometry)
η	Viscosity (apparent)
γ	Shear strain (%) (rheology)
σ	Shear stress

ω	Oscillation or angular frequency (rad/s)
$\Delta\rho$	Density difference
ρ	Density
τ	oscillation period
μm	Micrometre
λ_{max}	wavelength

Chapter 1

Introduction

At the present time, modified (controlled) release drug delivery systems are increasingly being developed and applied. The advantages of these products include their potential to optimise drug release rates to maintain blood drug levels and prolong therapeutic effects, to minimise side effects, decrease the number of daily administrations and improve patient compliance (Alderman 1984; Long & Chen 2009; Maderuelo et al 2011). Whilst the development of novel delivery systems and novel extended release materials are of increasing interest, commercial products often rely on established extended release technologies, such as pellets, osmotic pumps or hydrophilic matrices. Hydrophilic matrices are compressed mixtures of one or more water-swellaable hydrophilic polymers with a drug and other tablet excipients (Alderman 1984; Melia 1991; Li et al 2005). These dosage forms are popular because of their simple formulation, inexpensive cost, conventional production, ability to load high level drugs and good *in vitro-in vivo* correlations (Li et al 2005; Maderuelo et al 2011). Many natural, semi-synthetic and synthetic types of water-swellaable polymer have been used in hydrophilic matrices. Common examples include cellulose derivatives, sodium alginate, xanthan gum, polyethylene oxide, and carbopol. However, the most widely used are cellulose ethers (Melia 1991; Maderuelo et al 2011) and the many cellulose ether derivatives available, hydroxypropylmethylcellulose (HPMC) has perhaps become the most widely employed in hydrophilic matrix formulations (Siepmann & Peppas 2001; Li et al 2005; Maderuelo et al 2011). Studies of the effect of polymer grade and excipients are widespread, but this study will focus on the effect of organic anions used as drug counter ions, and some related short-chain surfactants, on certain HPMC solution and matrix release properties.

1.1. Cellulose ethers and derivatives

Cellulose is a linear polysaccharide in which β -D-glucose units are linked by β 1 \rightarrow 4 glycosidic bonds. Native cellulose has a highly crystalline structure arising from an extensive intramolecular and intermolecular hydrogen bonding network between linear polymer chains, and it therefore exhibits poor aqueous solubility. Ethers of cellulose are alkyl modifications of cellulose in which the hydrogen atoms of hydroxyl groups on the anhydroglucose unit are substituted by methyl, hydroxyethyl, hydroxypropyl, carboxymethyl or mixed ether groups. This chemical substitution disrupts the regular H-bonding arrangement and therefore destroys the crystalline properties of cellulose, resulting in an increased aqueous solubility as more side groups available for H-bond with water (Ott 1943; Donges 1990). Common cellulose ethers include methylcellulose (MC), hydroxyethylmethylcellulose (HEMC), hydroxypropylmethylcellulose (HPMC), ethylhydroxyethylcellulose (EHEC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), and sodium carboxymethylcellulose (NaCMC). Each derivative can be characterised by its degree of substitution (the average number of sites reacted per ring, DS) and molar substitution (the average number of alkylene oxide molecules reacted with each anhydroglucose unit, MS). The physical properties of these polymers are governed by the type and amounts of the substituent groups, for examples, their solubility depends on their DS and/or MS, with polar substituents strongly increasing hydrophilicity (Doelker 1987; Doelker 1993). Cellulose ethers have been known for their ability to sustain drug release since the earliest patent in 1962 (Christenson & Dale 1962) and they provide (i) a high ability to adopt desired drug release profiles (ii) a pH-independent matrix component (iii) a compatibility with conventional production techniques (iv) a broad FDA acceptance (or GRAS status) (Alderman 1984).

1.2. Hydroxypropylmethylcellulose (HPMC)

Hydroxypropylmethylcellulose (HPMC, hypromellose or Methocel™) is the water soluble, nonionic cellulose ether with hydroxypropyl and methyl substituent groups. The structure is shown in Figure 1.1. HPMC swells when hydrated, forming a gel which is stable over the range pH 3.0-11.0 (Doelker 1987; Doelker 1993; Li et al 2005). HPMC is perhaps the most commonly-employed cellulose ethers in hydrophilic matrices, as a gel-forming polymer which rapidly provides a surface hydrated polymer layer increasing the duration of drug release.

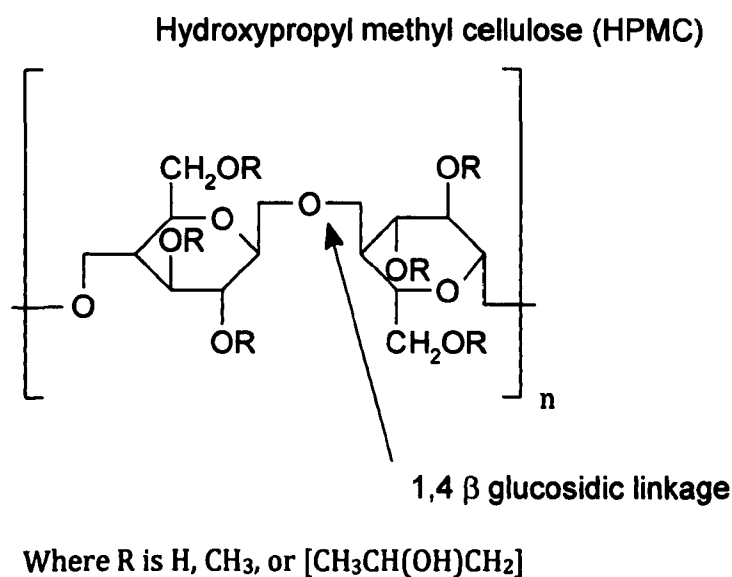


Figure 1.1 HPMC structure (after Wade 2000)

1.2.1. HPMC Types and applications

HPMC types are classified in the United States Pharmacopeia (USP) on the basis of their % methoxyl and % hydroxypropyl substitution. Methyl substitution is also characterized by degree of substitution (DS), which indicates the average number of methoxyl substitutions on a single glucose unit. As there are three available hydroxyl groups for substitution, then DS=0 for native cellulose and DS=3 for a completely substituted polymer. However, the number of hydroxypropyl substitutions on the anhydroglucose units is defined in terms of molar substitution (MS) because additional hydroxypropyl substitutions can occur on backbone-substituted hydroxypropyl groups. The distribution of the substituent groups along the cellulose chain can also influence the physiochemical properties of the HPMC (Viriden et al 2009a). As a result, each HPMC type exhibits different characteristics with respect to polymer properties that depend on substitution, for example, the sol:gel transition temperature (SGTT) or 'thermal gelation temperature' (Doelker 1987; Doelker 1993; Li et al 2005). The USP types of HPMC and their characteristics are listed in Table 1.1. The rank order of hydration rate has been indicated by Doelker (Doelker 1987) to be:

HPMC 2208 > HPMC 2910 > HPMC 2906 > MC

Companies worldwide manufacture pharmaceutical grade HPMCs. The HPMCs used in this thesis were manufactured by The Dow Chemical Company under the brand name Methocel™. This is probably the most widely used range in hydrophilic matrices. Methocel™ A is methylcellulose, while E, F, and K are HPMCs with different substitution levels that comply with USP specifications (Figure 1.2). The current study used HPMC E4M CR and HPMC K4M CR where "E" and "K" identify the substitution, "4" identifies the viscosity of 2% w/w solution at 20°C in millipascal-seconds (mPa.s), "M" designates the viscosity factor of 1,000x, and "CR" identifies controlled release (Dow Chemical Company 2002a). Controlled-release dosage forms mainly use HPMC K and E grade (Li et al 2005).

USP polymer type	MC	HPMC 2910	HPMC 2906	HPMC 2208
Dow Chemical type	Methocel A	Methocel E	Methocel F	Methocel K
Methoxyl content (%)	27.5 – 31.5	28.0 – 30.0	27.0 – 30.0	19.0 - 24.0
Hydroxypropyl content (%)	-	7.0 – 12.0	4.0 – 7.5	4.0 – 12.0
DS methoxyl	1.8	1.9	1.8	1.4
MS hydroxypropyl	0	0.23	0.13	0.21
Viscosity range of 2% solution (mPa.sec)	15 – 4000	5 – 4000	50 – 4000	100 – 100000
SGTT of 2% solution (°C)	50 - 55	58 - 64	62 - 68	70 - 90
Surface tension (mN/m) ^b	47 -53	44 - 50	44 – 50	50 – 56
Interfacial tension (mineral oil) (mN/m) ^b	19 - 23	18 - 19	19 - 23	26 – 28

Table 1.1 Substitution levels and important physical properties of different HPMC types (Doelker 1987; Doelker 1993; Li et al 2005; Dow Chemical Company 2002a).

MC = Methyl cellulose
HPMC = Hydroxypropylmethylcellulose
DS = Degree of substitution
SGTT = Sol:gel transition temperature
^a Tested with diluted solutions at 25°C, for Methocel with viscosity grades below 500mPa.s

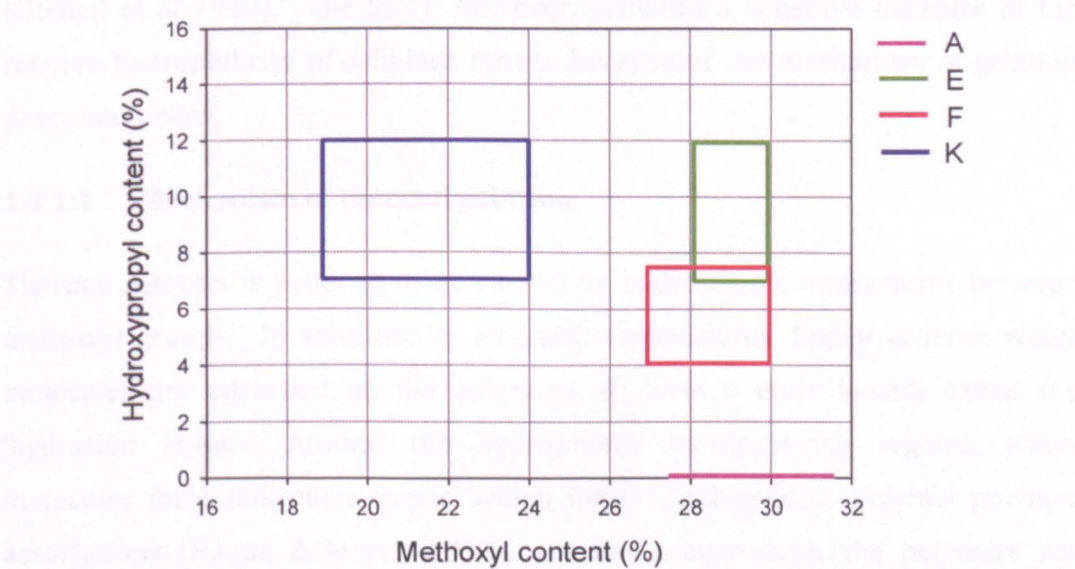


Figure 1.2 The substitution ranges of commercial Methocel™ HPMC grades. A=methylcellulose, E=HPMC (USP 2910), F=HPMC (USP2906) and K=HPMC (USP 2208). (Taken from Dow Chemical Company 2002a).

1.3. The properties of HPMC solutions

1.3.1. Thermal gelation

Most cellulose ethers solutions show a specific property called 'thermal gelation' or 'thermogelation'. This property is a reversible sol:gel transition in which a structured gel is formed when the temperature is elevated, which reverts to solution when cooled (Sarkar 1979; Doelker 1987). Repeating the heating and cooling cycle has no significant effect on gel or solution properties (Haque & Morris 1993) and the sol:gel transition temperature (SGTT) can be detected by changes in solution viscosity and solution turbidity. Sarkar (1979) has defined three different temperatures that can be used to measure this event: (i) the incipient gelation temperature (IGT) which is the temperature at which the viscosity reaches a minimum (ii) the incipient precipitation temperature (IPT), the temperature at which light transmission reduces to 97.5% and (iii) the cloud point (CPT) the temperature at which light transmission reduces to 50%. The rheological and turbidimetric end-points are not always coincident. At high concentrations, a gel often forms before turbidity occurs, whilst at low concentration a turbid solution can be observed before gelation (Sarkar 1979; Mitchell et al 1990). The SGTT, however, provides a sensitive measure of the relative hydrophilicity of cellulose ethers, because of the mechanism of gelation described below.

1.3.1.1 Mechanism of thermal gelation

Thermal gelation is believed to be caused by hydrophobic interactions between methoxyl groups. In solutions at ambient temperatures, highly ordered water molecules are adsorbed on the polymers, to form a layer loosely called the 'hydration sheath'. Around the hydrophobic methoxyl-rich regions, water molecules form molecular 'cages' which inhibit hydrophobic polymer-polymer associations (Haque & Morris 1993). At low temperature, the polymers are hydrated and there is little polymer-to-polymer interaction other than simple entanglement. As the temperature is raised, polymer molecules lose water of hydration, when the sol:gel transition temperature (SGTT) has been reached.

Dehydration of the polymer is sufficient to allow association of hydrophobic domains (methoxyl-rich regions). These areas form 'junction zones' and their hydrophobicity causes the exclusion of local water, resulting in a progressive decrease in polymer solubility. This leads to the formation of a 3-dimensional gel network stabilised by intra- and inter-polymer hydrophobic interactions and the solution forms a gel which often phase separates (Sarkar 1979; Doelker 1993; Haque & Morris 1993; Sarkar 1995; Hirrien et al 1998; Silva et al 2008). Both single chains and large aggregates are found in polymer solutions at low temperature whereas only large aggregates appear in solutions above the SGTT (Zhou et al 2008).

Figure 1.3 shows a schematic illustration of the proposed mechanism according to Haque et al (1993), who investigated the gelation of MC and HPMC using oscillatory rheology, differential scanning calorimetry, ^1H -NMR and light scattering, and were the first to propose a two-stage gelation process. The first stage was attributed to the unfolding of cellulose bundles on the terminal ends of polymer chains, whilst the second stage was attributed to the disruption of polymer hydration sheaths and the formation of a 3-dimensional gel network (Haque & Morris 1993; Haque et al 1993). This proposal is supported by the work of Bajwa et al (2009) using ATR-FTIR to monitor changes in the vibration of chemical bonds in HPMC solutions during the sol-gel transition.

A different postulate has been suggested by Kobayashi et al (1999) who investigated the gelation of MC using light scattering, oscillatory rheology and small-angle neutron scattering. They claimed that the first stage of gelation can be attributed to the dehydration of the hydration sheaths by heating and the formation of hydrophobic associations, whereas the second stage can be attributed to the phase separation of these hydrophobic regions from solution, leading to the formation of the 3-dimensional gel. Buslov et al (2008) also studied thermal gelation of MC using FTIR-ATR and found that the formation of a 3-dimensional gel network not only resulted from hydrophobic association of methoxyl substituents but also from inter-chain H-bonds involving unsubstituted primary hydroxyl groups accompanied by a conformational change of the polymer backbone.

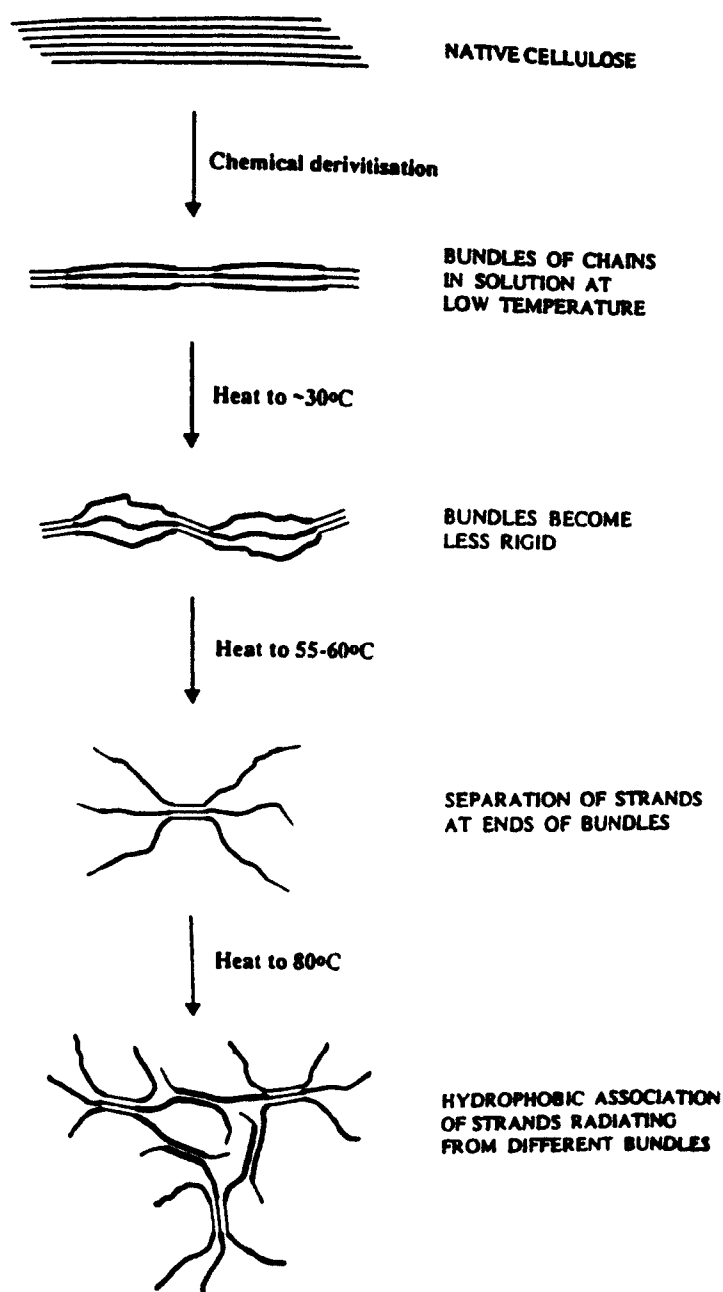


Figure 1.3 Schematic illustration of the postulated structures and processes involved in the thermal gelation of MC (HPMC A4M) (from Haque & Morris 1993). Faint lines denote unsubstituted or sparingly-substituted chain segments; bold lines denote regions of dense substitution.

1.3.1.2 Factors affecting the sol:gel transition of cellulose ethers

(a) Type, degree and uniformity of substitution

The type, degree and uniformity of substitution are important factors in the behaviour of cellulose ether derivatives. Increasing the degree of methoxyl substitution usually results in a decrease in SGTT because hydrophobic interactions can increase (Sarkar 1979; Sarkar 1995). On the other hand, increasing the hydroxyalkyl substitution can increase SGTT because this group can hydrogen bond with water and inhibit intermolecular association (Doelker 1987; Haque & Morris 1993; Haque et al 1993). The degree of hydrophobic junction zone formation is reflected in the gel strength and their SGTT. It has been reported that above the SGTT, MC forms a firm gel whereas HPMC E and F, which are more hydrophilic, form semi-firm gels. The most hydrophilic forms of pharmaceutical HPMC, the K grades, form a mushy gel with no measurable strength (Sarkar 1979). The SGTT values are shown in Table 1.1. Hirrien et al (1996) have reported that MC exhibited different behaviour as a function of temperature depending on the DS values, intermolecular interactions occurred at $T > 45^{\circ}\text{C}$ when $\text{DS} > 1.5$, but there was no clear evidence for aggregation at this temperature when $\text{DS} < 1.5$. Viriden et al (2009b) has claimed that more heterogeneously substituted polymers exhibit a higher SGTT and slower rates of gelation and suggested this arises from their amphiphilic properties, resulting in a reduced capacity of dehydration from the polymer and the delay of hydrophobic aggregation.

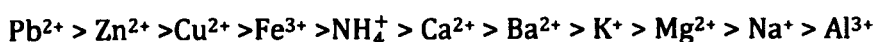
(b) Molecular mass and polymer concentration

There appears to be little relationship between molecular mass of the polymer and SGTT (Sarkar 1979). The viscosity of HPMC solutions increases with HPMC concentration (Silva et al 2008) but the IGT, IPT and CP have been also shown to vary considerably with polymer concentration. Values of IPG and CP decrease with increasing concentration until a critical concentration is reached. High polymer concentrations (over the critical limit) can decrease SGTT, but gel formation occurs before turbidity is observed. In contrast, at low polymer

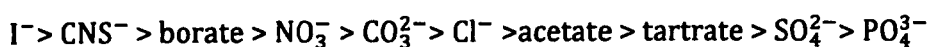
concentrations turbidity can occur before gel formation (Sarkar 1979; Li et al 2005).

(c) Presence of additives

In solutions, HPMC is a hydrated colloid and is susceptible to 'salting out' from solution by solutes (Sarkar 1979; Nakano et al 1999). Inorganic salts, electrolytes and most water-soluble substances (e.g. sorbitol, sucrose, glycerol), depress SGTT by competing for the available water, dehydrating the polymer hydration sheath, and thus favouring polymer-polymer interactions. This 'salting-out' efficiency varies widely for different cellulose derivatives and depends on the nature of both the cations and anions (Alderman 1984; Doelker 1987; Mitchell et al 1990; Doelker 1993; Li et al 2005). Nonionic cellulose ethers tolerance for cations has been ordered as follows:



For anions, the rank order is :



Ion tolerance generally follows the classical order of Hofmeister's series. The amount and the length of the hydrophobic alkyl substituent will modify the salt tolerance and hydroxyalkylation will enhance the electrolyte concentration limit for gelation. (Touitou & Donbrow 1982b)

Conversely, certain large ions (e.g. basic drugs) may raise SGTT by adsorption of these ions, which carry water, onto the polymer leading to an overall increase in polymer hydration. Some drugs can also affect SGTT, for examples, MC has been reported to interact with tetracaine hydrochloride and dibutoline sulphate; HEMC and HEC have shown association tendencies with phenothiazine tranquilisers; NaCMC reacts with certain cationic drugs (Doelker 1987; Li et al 2005).

Solvents such as ethanol, polyethyleneglycol (PEG), and propylene glycol (PG) can raise SGTT (Doelker 1987; Dow Chemical Company 2002a). L-amino acids can lower SGTT if they are small hydrophilic molecules, and raise SGTT if they are large, hydrophobic or aromatic molecules (Richardson et al 2006).

Surfactants also interact with cellulose ethers. The addition of sodium dodecyl sulphate (SDS) was found to increase the SGTT of HPMC solutions by solubilising the methoxyl rich “junction zones” which are responsible for aggregation and precipitation, thereby leading to an increase in solubility of the polymer (Nilsson 1995). The increase of polymer hydrophobicity induced polymer-surfactant aggregation (Evertsson & Nilsson 1998).

The abilities of additives to depress or elevate the cloud point, or salt out the polymer can be expressed as the constant K_{CP} , which can be calculated from the relationship in Equation 1.1.

$$\log CP = \log CP_0 + K_{CP}m \quad \text{Equation 1.1}$$

CP is the observed cloud point, CP_0 is the theoretical cloud point in absence of additive and m is the molar concentration.

(d) Experimental conditions

In rheological studies, higher shear rates corresponding to non-Newtonian regimes, can prevent gelation and cause SGTT to be raised to higher temperatures (Silva et al 2008). It has also been reported that SGTT may be affected by heating and stirring rate (Doelker 1993).

1.3.2. Rheology

Cellulose solutions exhibit the typical rheological behaviour of linear polymers. The viscosity of cellulose ether solutions is dependent on their concentration, molecular weight and substitution. The molecular weight is controlled during manufacture through exposure to the air, leading to oxidation and cleavage of the glycosidic bonds in the polymer chains (Donges 1990). Above a certain concentration, non-ionic ether solutions, especially low molecular weight cellulose derivatives, tend to be thixotropic and exhibit a time-dependent reduction of viscosity under fixed flow conditions (Doelker 1987). Above the critical entanglement concentration, polymer chains show an equal rate of entanglement

and disentanglement at low shear, giving rise to Newtonian-like properties. At higher shear rates, HPMC forms fewer polymer associations between consecutive shear deformations, and shows evidence of shear thinning (Haque et al 1993). Thuresson and Lindman (1999) have suggested that the viscosity of cellulose ether solutions may be attributed to polymer entanglements in the short term and to strong associations between unsubstituted regions of the native cellulose in the longer term. These interactions are thought to arise from strong hydrogen bonds between unsubstituted hydroxyl groups. The viscosity of polymer solutions is also affected by temperature and additives (e.g. electrolytes and other solutes) whereas the solution pH (in a range of pH2-12) has no practical effect on the viscosity of nonionic cellulose ethers (Doelker 1987). Table 1.1 shows the viscosity range of 2% solutions for commercially available grades of HPMC.

1.3.3. Surface activity

HPMC and other cellulose ethers contain hydrophobic (alkyl) and hydrophilic (hydroxyl) side groups so that they can reduce the surface tension of water and the interfacial tension of aqueous systems. The degree of surface activity is dependent on the distribution of these groups along the cellulose backbone and the relative balance of the substituent groups, whereas concentration has little effect (Sarkar 1984; Doelker 1987). The total surface free energy was generally assimilated to the surface tension of a polymer solution in the range of concentration independence whereas the non-polar and polar contributions were obtained from contact angle measurements. Table 1.1 shows the surface tension and interfacial tension on mineral oil, of dilute HPMC solutions in which the surface tension of the aqueous solution is 72.0mN/m at 25°C and the interfacial tension on mineral oil is ~41mN/m for pure water (Doelker 1987). HPMC 2910 exhibits a greater ability than HPMC 2208 to reduce surface tension and interfacial tension because HPMC 2910 has more methoxyl substitution.

1.4. The properties of HPMC matrices

1.4.1 Hydrophilic matrices

A hydrophilic matrix is a solid extended release dosage form comprising of a mixture of ingredients including one or more water-swellaable hydrophilic polymers. This matrix may be compressed to tablets, or filled in hard shell capsules. HPMC is one of the most popular polymers used to incorporate into a matrix tablet to provide extended release and it has become the 'industry-standard' material for hydrophilic matrices (Alderman 1984; Li et al 2005).

1.4.2 Mechanism of drug release

Figure 1.4 shows the principal mechanisms of drug release from a hydrophilic matrix tablet. When the matrix is exposed to a liquid medium, rapid diffusion of medium into the matrix tablet will occur and lead to the hydration and relaxation of polymer chains, followed by the formation of a continuous layer of concentrated hydrated polymer around the tablet surface, commonly termed the 'gel' layer (Alderman 1984; Ford 1999; Siepmann et al 1999). Within the gel layer is a concentration gradient of polymer, water soluble and it is a complex aggregate of water, water-soluble polymer, drug and excipients (Alderman 1984; Fyfe & Blazek 1997). The gel layer expands and increases in thickness with time as the medium penetrates. At the same time, there is disentanglement of polymer chains at the surface of the gel layer and polymer release in the stirred medium, a process collectively known as 'erosion' (Colombo 1993). The gel layer acts as a diffusion barrier to control both the water uptake and the release of drugs (Colombo et al 2000). During the early stages of hydration (gel layer formation) drug on the tablet surface is rapidly released into the hydration medium as an 'initial burst' whereas subsequent drug release is controlled by the gel layer and occurs more slowly. The simple view is that the release mechanism from the matrix is diffusion-controlled in the case of water-soluble drugs, and erosion controlled in the case of intermediate and poorly drugs (Alderman 1984; Linhardt 1989; Li et al 2005). The release rate of water-soluble drugs mainly depends on diffusion rate through the gel whereas the release rate of water-insoluble drugs depends on the

rate of mechanical erosion from the surface gel layer. However, most drugs with aqueous solubility are considered to be released simultaneously by diffusion and erosion processes (Gao et al 1996; Kim & Fassihi 1997a).

The critical processes in the drug release mechanism has been described by Colombo et al (1995; 1999a; 1999b; 2000) who initially used an optical microscopy method to visualise the distribution of a coloured, water-soluble drug (buflomedil pyridoxal phosphate) within an HPMC matrix tablet. Figure 1.5 shows a schematic illustration of a cross-sectioned hydrated HPMC matrix tablet in which Colombo et al identified three moving fronts within the gel layer. These fronts separate (i) the outer matrix and medium (erosion front), (ii) the glassy/ rubbery polymer transition (swelling front) and (iii) the solid drug and hydrated drug (diffusion front). In the beginning of gel layer formation, the gel thickness is small so that medium ingress into the dry matrix core occurs rapidly, and there is rapid inward movement of the swelling front and expansion of the gel (Colombo 1993). Water-soluble drugs, which are mainly released by diffusion, will exhibit initially a fast release rate of release because of the short diffusional distance across the thin gel layer, however, the release rate becomes progressively slower as the gel layer expands and will exhibit release linear with root time kinetics. On the other hand, water-insoluble drugs, which are primarily released through the relaxation and dissolution of polymer chains at the erosion front (including the mechanical removal by shear forces) exhibit zero-order drug release (Colombo et al 2000).

The ability of the gel layer to retard water penetration means that these processes occur over a prolonged time extended release of drug is achieved. However, a poorly formed gel, in which the diffusion barrier layer is disrupted or incompletely formed, will permit a more rapid medium ingress, leading to more rapid drug release and in more extreme cases, the premature disintegration of the matrix (Li et al 2005).

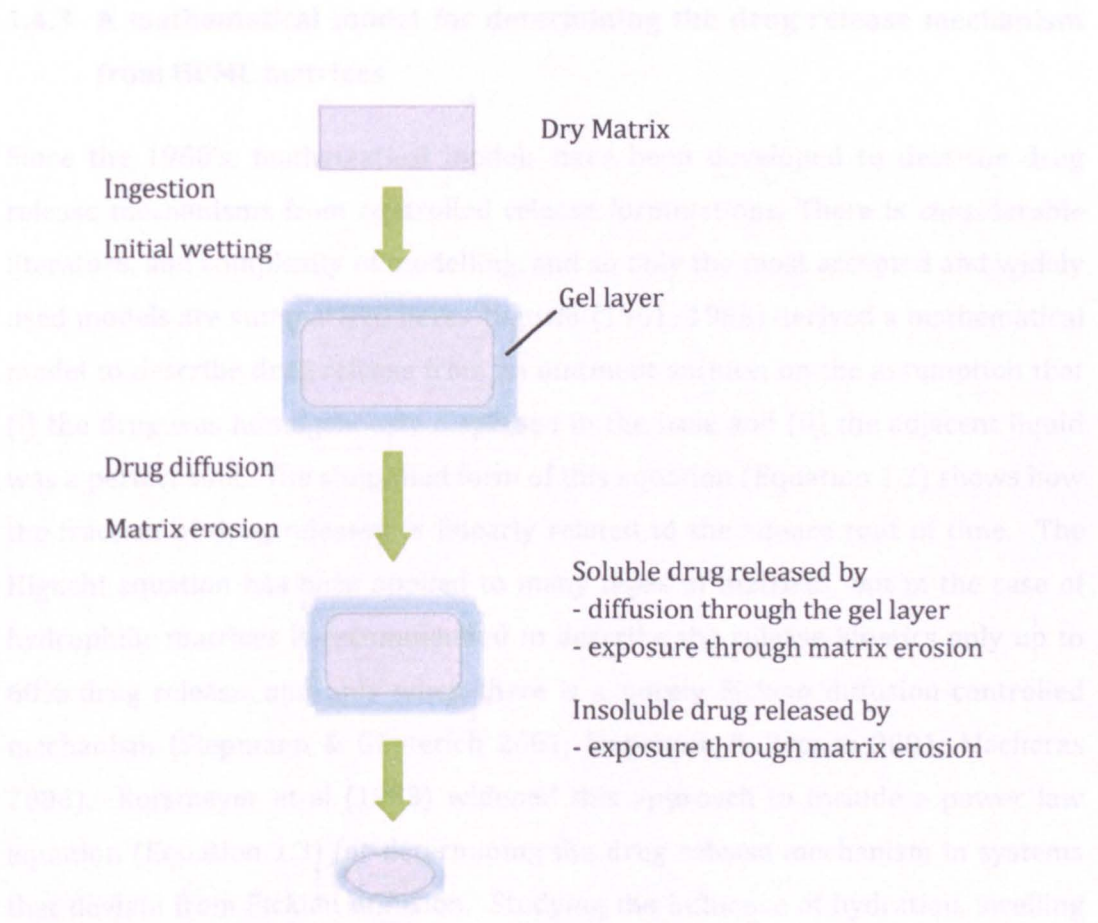


Figure 1.4 The principal drug release mechanism of a hydrophilic matrix tablet
(Adapted from Alderman 1984)

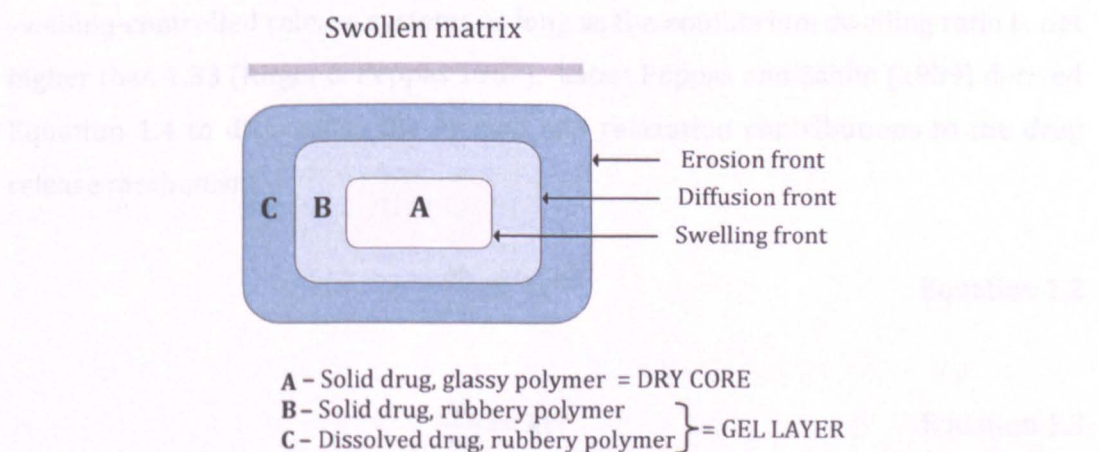


Figure 1.5 Schematic illustration of a cross-section HPMC matrix tablet during hydration and drug release. Three moving fronts are identified and the matrix is divided into three regions by the hydration stage of the polymer and drug (Adapted from Colombo et al (1995)).

1.4.3 A mathematical model for determining the drug release mechanism from HPMC matrices

Since the 1960's, mathematical models have been developed to describe drug release mechanisms from controlled release formulations. There is considerable literature, and complexity of modelling, and so only the most accepted and widely used models are summarised here. Higuchi (1961; 1963) derived a mathematical model to describe drug release from an ointment surface, on the assumption that (i) the drug was homogenously dispersed in the base and (ii) the adjacent liquid was a perfect sink. The simplified form of this equation (Equation 1.2) shows how the fraction of drug released is linearly related to the square root of time. The Higuchi equation has been applied to many types of matrices, but in the case of hydrophilic matrices is recommended to describe the release kinetics only up to 60% drug release, and only when there is a purely Fickian diffusion-controlled mechanism (Siepmann & Göpferich 2001; Siepmann & Peppas 2001; Macheras 2006). Korsmeyer et al (1983) widened this approach to include a power law equation (Equation 1.3) for determining the drug release mechanism in systems that deviate from Fickian diffusion. Studying the influence of hydration, swelling and glass transition (T_g) of the polymer, it has been concluded that the release mechanism depended principally on diffusion, gel erosion and polymer relaxation (Peppas 1985; Siepmann & Göpferich 2001). Equation 1.3 can be used to analyse swelling-controlled release systems as long as the equilibrium swelling ratio is not higher than 1.33 (Ritger & Peppas 1987). Later, Peppas and Sahlin (1989) derived Equation 1.4 to distinguish the Fickian and relaxation contributions to the drug release mechanism.

$$\frac{M_t}{M_\infty} = kt^{0.5} \quad \text{Equation 1.2}$$

$$\frac{M_t}{M_\infty} = kt^n \quad \text{Equation 1.3}$$

$$\frac{M_t}{M_\infty} = k_1t^m + k_2t^{2m} \quad \text{Equation 1.4}$$

In these equations, M_t is the amount of drug released at time t , M_∞ is the amount of drug released at infinite time, k_1 and k_2 are kinetic constants, t is the release time and n and m are diffusional exponents which have been used to describe the release mechanism. In the case of Equation 1.4, the first term describes the Fickian contribution, and the second term describes Case II relaxation. The diffusional exponent can range from 0.43 to 1 depend on the release mechanism and the shape of the drug delivery device, and the drug transport mechanism can be classified as in Table 1.2 (Peppas 1985; Peppas & Sahlin 1989; Peppas & Colombo 1997; Costa & Lobo 2001; Maderuelo et al 2011). This model assumes that drug release will start immediately after the matrix is exposed to solution, and the mechanism of drug release is constant during the first 60% of cumulative release.

Diffusional exponent (n)	Type of drug transport
$n = 0.5$	Fickian diffusion
$0.5 < n < 1.0$	non-Fickian or anomalous transport
$n = 1.0$	case II transport
$n > 1.0$	super case II transport or zero-order release kinetics

Table 1.2 The category of drug transport from the controlled release matrices classified by the diffusional exponent (n).

Later, Ford et al (1987) showed that drug release rarely passed through the origin and the equation should therefore incorporate a lag time. The lag time account for the time required for the matrix perimeter to hydrate and the gel layer to reach equilibrium, before the advance of the solvent front through the matrix and erosion of the surface, predominates (Ford et al 1991a). Equations 1.3 and 1.4

have been modified to account for the lag time (l) in Equations 1.5 and 1.6 respectively.

$$\frac{M_t}{M_\infty} = k(t - l)^n \quad \text{Equation 1.5}$$

$$\frac{M_t}{M_\infty} = k_1(t - l)^n + k_2(t - l)^{2n} \quad \text{Equation 1.6}$$

Other models which have been used in the literature but not investigated here included the Hixson-Crowell model and the zero-order equation. These have been traditionally used for poorly soluble drugs (Costa & Lobo 2001). More complex models have been developed by various authors, most notably Siepmann (Siepmann et al 1999; Siepmann et al 2000; Siepmann & Peppas 2000; Siepmann & Göpferich 2001; Siepmann & Peppas 2001).

1.4.4 Factors affecting matrix drug release

There are numerous factors which affect drug release from HPMC matrices and the most important can be divided into polymer and non-polymer factors.

1.4.4.1 Polymer factors

(a) Polymer hydration rate

Rapid hydration and formation of a protective gelatinous layer are necessary to control drug release from a hydrophilic matrix and the gel layer must form more rapidly than the dissolution of drugs and excipients (Alderman 1984; Li et al 2005). Alderman (1984) has described that the relative hydration rate of HPMC was related to the amount of hydrophilic (hydroxyl and hydroxypropyl substituents) on the cellulose backbone and only HPMC 2208, the most hydrophilic and rapidly-hydrating polymer, provided significant sustained release. However, the matrix in the Alderman studies contained only 10%w/w HPMC, below what is regarded as a threshold polymer content, and so these experiments may have been unduly discriminating. Mitchell et al (1993b) investigated at the

higher and more normal HPMC levels (~30%w/w HPMC) and found no relationship between the proposed hydration rates of HPMC grades and the rate of drug release from matrix tablets. Rajabi-Siahboomi (1993) who investigated the swelling and hydration rate of different HPMC grades using ^1H -NMR microscopy also found no relationship between Methocel™ grade and hydration and swelling rate between HPMC types.

(b) Polymer viscosity

The viscosity of cellulose ethers is a function of their molecular weight and increasing the viscosity grade of the polymer, leads to a more viscous and higher gel strength gel layer. Thus the resistance to polymer erosion is greater and drug diffusion is slower (Alderman 1984; Reynolds et al 1998; Velasco et al 1999; Li et al 2005; Maderuelo et al 2011). This has been attributed to their increased hydrodynamic volume occupied by the higher molecular weight polymer chains (Wan et al 1991; Wan et al 1993; Gao et al 1996). With an increased HPMC, viscosity the percentage of swelling increases whilst the percentage of erosion decreases (Ravi et al 2008). This leads to the slower release of both water-soluble and poorly soluble drugs and high-viscosity HPMC is recommended for water-soluble drugs to achieve release kinetics controlled by diffusion whereas low-viscosity HPMC is recommended for sparingly water-soluble drugs to achieve sufficiently fast release kinetics in which erosion predominates (Tahara et al 1995; Gao et al 1996; Hiremath & Saha 2008; Mitchell & Balwinski 2008; Ravi et al 2008; Maderuelo et al 2011).

(c) Polymer concentration

Generally, an increase in the polymer concentration in the matrix corresponds to a lower porosity of the matrix, and thus drug release rate decreases (Reza et al 2003; Ebube & Jones 2004). Mitchell et al (1993d) suggested that an increase in the polymer concentration elicits a greater degree of cross-linking of the polymer

side chains, leading to the increase in gel tortuosity which can slow down diffusion of drug across the gel layer. High polymer contents lead to a thicker and more viscous gel formation whereas low polymer levels result in slower gel formation, Increasing polymer concentration, produces gel layers more resistant to diffusion or erosion and thus drug release is slower (Alderman 1984; Doelker 1987; Li et al 2005). The minimum concentration of HPMC required for a hydrophilic matrix to rapidly form an effective gel layer and barrier to medium ingress is considered to be approximately 20%w/w (Goncalves-Araujo et al 2008). At polymer contents higher than 20%w/w, the variations in the degree of viscosity and particle size of the polymer do not cause important changes in drug release. This emphasises the greater importance of the polymer content in comparison with polymer viscosity and particle size in determining drug release rate (Campos-Aldrete & Villafuerte-Robles 1997). However, formulations that contain 30-40%w/w HPMC tend to exhibit exhibited the similar drug release profiles independent of HPMC grades and diluents, and is more widely accepted to be the level at which drug release from the HPMC matrix becomes less dependent on other factors (Li et al 2005).

The drug/polymer ratio has also been considered as an important factor controlling drug release (Ford et al. 1985b; Ford et al. 1987). In the case of water-soluble drugs, the system becomes more porous as drug loads increase with respect to the polymer, leading to faster release rates (Siepmann & Peppas 2000). Dabbagh et al (1996) similarly found that the drug release rate increased as the polymer fraction was decreased.

(d) Polymer Substitution

At low polymer levels, drug release rates depend on HPMC substitution type. The hydrophobic methoxyl groups can retard hydration as they decrease H-bonding within and between particles of close proximity, especially the dry regions. The different substitution levels also gave rise to different water mobilities, leading to different drug release characteristics (Mitchell et al 1990b; Mitchell et al 1993b; Li et al 2005; Rajabi-Siahboomi et al 1996a). Haque and Morris (1993) reported that

as the hydroxypropyl content of HPMC was increased, a weaker gel was formed which was more susceptible to erosion. This resulted in faster drug release (Dahl et al 1990; Haque & Morris 1993). The interaction between cellulose ethers and water, results in three types of water being present in a hydrated HPMC gel: (i) free water (no binding), (ii) interface water (weakly polymer-bound), and (iii) bound water (strongly bound to the polymer). The proportions of these types of water depend on the polymer substitution (Jhon & Andrade 1973).

(e) Polymer particle size

HPMC particle size and size distribution have been shown to significantly affect the hydration rate of polymer and drug release from matrices. Smaller particle size fractions of HPMC exhibit a higher surface area to the hydration medium, leading to a rapid gel layer formation and often better extended release properties (Heng et al 2001). At low polymer content, it has been found that the drug release rate decreased as HPMC particle size was reduced, whereas drug release rate increased when HPMC particle size increased. With the extremely large particle sizes burst release can occur but conversely, reductions in particle size below 150 μ m caused no further decrease in dissolution rate (Mitchell et al 1993c; Campos-Aldrete & Villafuerte-Robles 1997; Li et al 2005). Faster release or burst release from large particle sized polymer has been attributed variously to a decrease in tablet compressibility, matrix water uptake, polymer swelling, gel layer viscosity and gel layer formation rate (Alderman 1984; Rajabi-Siahboomi 1993; Nokhodchi et al 1995; Velasco et al 1999). Heng et al 2001 have reported that above a critical mean HPMC particle size, the release mechanism deviates from first order kinetics and that polymer size distribution affected drug release rate but not the release mechanism.). Mitchell and Balwinski (2007) found that HPMC particle size and particle size distribution influenced drug release and release mechanism only when less than 50% of HPMC was smaller than 63 μ m for the ranges studied.

1.4.4.2 Non-polymer factors

(a) Drug factors

Properties of incorporated drugs that can affect drug release rate form an HPMC matrix include particle size, molecular weight and solubility (Li et al 2005; Maderuelo et al 2011). Ford et al (1985a; 1985b) found that increasing the particle size of water-soluble drugs (propranolol hydrochloride, promethazine hydrochloride and aminophylline) lead to slower release rates, but this occurred only at low polymer content. In the case of poorly soluble drugs (e.g. indomethacin), increased particle size resulted in decreased release rates. It was proposed that this was simply the result of the slower dissolution of larger particles as the drug surface area to volume ratio was decreased (Ford et al 1985c). In contrast, Hiremath and Saha (2008) found faster (insoluble) rifampicin release with increasing drug particle size. It was suggested that this was the result of polymer depleted regions within the matrix which were rich with large drug particles.

Talukdar et al (1996) suggested that water-soluble drugs with lower molecular weight will diffuse more rapidly through the gel layer and exhibit longer mean dissolution times than higher molecular weight drugs. They also found that the release of water-soluble drugs was faster than the release of water-insoluble drugs which the authors attributed to their different release mechanisms. Tahara et al (1996) described the relationship between drug solubility and release mechanism which was explained in terms of three scenarios : (i) with poorly water-soluble drugs, the drug dissolution rate is slower than the erosion rate and as a result matrix erosion is the limiting process in drug release, (ii) in the case of drugs with a solubility between 0.5mg/ml and 5mg/ml, the dissolution rate is dependent on both the matrix erosion rate and the medium penetration rate as the dissolution rate increases with the increase in the drug solubility, and (iii) for highly water-soluble drugs (>5mg/ml), the dissolution rate is similar to the rate of medium penetration. High solubility drugs can increase drug release rates through both diffusion and erosion mechanisms by acting as microcavities in the gel layer,

making the gel structure more porous and weaker (Doelker 1987; Linhardt 1989; Yang & Fassihi 1997; Li et al 2005). However, some studies found that use of some water-soluble drugs leads to a slower drug release, and postulated that they may aid rapid gel formation, whereas poorly soluble drugs cannot contribute in this way (Mitchell et al 1993a; Mitchell et al 1993d).

Drug release kinetics depend not only on drug diffusion and matrix erosion, but also on the relaxation of the polymer, the dissolution rate of drugs in the gel layer (Colombo & Bettini 1999a) and solid drug translocation in the gel due to polymer swelling (Bettini et al. 2001). More soluble drugs will be more available because they dissolve more extensively in the limited water within the gel layer, but poorly soluble drugs which slowly dissolved in the gel layer will allow drug particles to be transported close to the matrix erosion front. If there was a considerable amount of solid drug particles remained in the gel phase when the matrix had been completely hydrated, the erosion became accelerated.

In the case of matrices containing a high content of high solubility and drugs, significant burst release can occur from drug at or near the matrix surface being release immediately after matrix contact with the dissolution medium. Hence very high drug release rates can be seen during the first few hours when dissolution testing these types of formulations (Batycky et al 1997; Brazel & Peppas 1999; Velasco et al 1999; Huang & Brazel 2001).

(b) Additives

Many studies have shown how diluents can modulate drug release from hydrophilic matrices and although it has been reported that generally an increased amount of diluents involve an increase in drug release rate, this is usually a result of a lowering HPMC content (Lotfipour et al 2004). Early studies described by Alderman (1984) compared drug release from HPMC matrices containing a soluble diluent (lactose) with those containing a swellable insoluble diluent (microcrystalline cellulose or MCC) and a non-swellable insoluble diluent (dicalcium phosphate). Matrices containing swellable insoluble diluents exhibited greater initial burst drug release (compared with those containing soluble

diluents) but provided slower drug release afterwards. It has been suggested that the presence of even small amount of fibrous insoluble diluents may prevent homogeneous gel layer formation (Zuleger & Lippold 2001; Zuleger et al 2002). In a more extreme example, superdisintegrants have, not surprisingly, been found to increase the drug release rate from matrices (Li et al 2005)

In contrast, dicalcium phosphate, the non-swelling insoluble diluent was found by Alderman to prevent the formation of a coherent gel layer, and destroy the extended release properties of the HPMC matrices. However, these formulations contained very low polymer content (10%w/w HPMC) and are hardly typical. Subsequently, many authors reported no problems in gel formation with dicalcium phosphate (Ford et al 1987; Rekhi et al 1999). Rekhi et al (1999) also found that HPMC matrices containing a soluble diluent, lactose exhibited faster release than those with insoluble dicalcium phosphate which was attributed to dissolving of the lactose decreasing gel strength. Levina and Rajabi-Siahboomi (2004) have described how a grade of partially pregelatinised starch (Starch 1500®) decreased drug release rate in comparison with HPMC matrices containing MCC (swellable but insoluble) and lactose (soluble) diluents. Myles et al (2005; 2006) has shown how Starch 1500, which is partially swellable, contributes physically to the gel layer structure, and can increase the robustness of low polymer HPMC matrices to ionic challenge.

Sheskey et al. (1995) and Rekhi et al (1999) reported that magnesium stearate content over the range 0.2 and 2% w/w had no effect on drug release. However, at higher lubricant levels, we would expect that magnesium stearate would cause the commonly reported reduction in tablet tensile strength, and drug release may be increased if the tablet became sufficiently weak to be more permeable.

Weak acid pH-modifying excipients (fumaric, sorbic and adipic acid) when incorporated into HPMC matrices with the resulted in significant increases in the release of weakly basic drugs in pH 6.8 and 7.4 phosphate buffers (Kranz et al 2005). In a similar way, alkalizing buffers such as sodium citrate and THAM can aid release of a weak acid drug (felbinac) in acid media (Pygall et al 2010). These

effects resulted from a temporary localised pH modification of the gel layer, but sodium citrate matrices were shown to further accelerated matrix release, probably a result of multivalent ionic disruption of the gel layer formation (Pygall et al 2009). These effects depend on the pKa and solubility of the pH modifiers for the case of weak acid modifiers. Fumaric acid, which has a lower pKa and is more slowly soluble, was more effective than sorbic and adipic acids in enhancing drug release, and provided a release profile that almost overlapped the same formulation at pH 1.2 and was independent on the amount of fumaric acid in the formulation (Streubel et al 2000; Varma et al 2005; Siepe et al 2006b). In the same way, THAM with a higher pKa, provided more prolonged buffering of a weak acid drug than sodium citrate (Pygall et al 2009; Pygall et al 2010).

Surfactants incorporated into the matrix can modify drug release (Ford et al 1991b) but explanations have focused on the potential for ion pair salt formation with the drug. For example, sodium dodecyl sulphate (SDS) incorporated in HPMC matrices could interact with propranolol hydrochloride, and decreased the release rate from HPMC matrices, whereas cetrimide showed an opposite effect (Nokhodchi et al 2008).

The inclusion of cyclodextrins with poorly-soluble drugs can result in faster release rates from HPMC matrices (Guo & Cooklock 1995). This can be explained by the improvement in solubility of these drugs in the presence of cyclodextrins, and is supported by the decrease in release rate found with water-soluble drugs, which is probably a result of the inclusion drug molecules in the cyclodextrin (Vueba et al 2004).

Ionic salts or water-soluble substances can also cause precipitation, or salting out of cellulose ethers by competing for the available water and dehydrating the polymer hydration sheath. In brief this will change the SGTT of cellulose ethers, the hydration rate of the polymer, and thus the dissolution profile of the matrix (Alderman 1984; Li et al 2005). A more comprehensive review of the influence of these types of pharmaceutical additives on HPMC solutions and HPMC matrices is provided in the introduction of Chapter 3, 4 and 5.

(c) Tablet shape and modification

The tablet surface area/volume ratio is one of the key factors in controlling drug release from HPMC matrix tablets. Drug release rate is linearly related to tablet surface area so that increased surface area leads to increased drug release rates. As a result, smaller tablets require a higher polymer content than larger tablets to achieve the same release profile with the same drug (Ford et al 1987; Li et al 2005). In addition, larger matrix tablets have slower release profiles because the core is thicker, and also, it is reported, the gel layer (Siepmann et al 1999; Siepmann et al 2000). When the tablet surface area/volume ratio was held constant, similar release profiles were obtained ($f_2 > 70$) (Reynolds et al 2002). Therefore, modifications of tablet shape which involve changes in the matrix surface area/volume ratio will inevitably lead to changes in drug release (Rekhi et al 1999). It has been reported that the influence of matrix shape and size on hydrophilic matrices is greater than that on hydrophobic matrices (Staniforth 2001).

(d) Tablet porosity

Air bubbles within the hydrated layer of hydrophilic matrices are formed during the swelling of the polymer. These bubbles arise from the void volume porosity of the matrix tablet and are an integral part of gel layer structure (Melia et al 1993). If present in large numbers, they could potentially lead to modulation of the release kinetics by increasing the tortuosity of the drug diffusion path. However, tablet porosity may not be a significant factor under normal circumstances as many studies show that drug release from HPMC matrices is independent of tablet compression pressure (Ford et al 1985a; Rekhi et al 1999; Velasco et al 1999). However, Levina and Rajabi-Siahboomi (2004) reported slower release of chlorphenamine maleate with increasing matrix compression pressure in a formulation that contained a low polymer content (20%w/w HPMC). Dabbagh et al (1996) found that their matrix formulations had similar porosities and dissolution profiles when manufactured above a threshold compression force (78.7 mNm^{-2}) whereas tablets manufactured below this value, had higher porosities.

and faster release rates. High compression pressures were postulated to reduce tablet porosity and the initial medium uptake, and therefore, reduce the initial burst of drug during the formation of a gel layer.

(e) Dissolution testing conditions

The ionic strength and temperature of the dissolution medium have all been found to influence drug release during USP dissolution testing. As non-ionic polymer HPMC is pH -insensitive, so that any direct pH effects (e.g. between simulated gastric fluid USP pH 1.2, simulated intestinal fluid USP pH 6.8) generally arise from the behavior of other components such as drug solubility (Bravo et al 2004). However, HPMC is sensitive to differences in ionic strength, and it has been shown that at high molar ion concentrations, or in the presence of other soluble such as dietary sugars, matrices exhibit accelerated drug release. This has been attributed to the decreased capacity of HPMC to form gel layer (Mitchell et al 1990a; Bajwa et al 2006; Xu et al 2006; Pygall et al 2009; Williams et al 2009). Ford et al (1991a) reported that when the temperature of the dissolution medium is increased, the faster release of promethazine hydrochloride from HPMC matrices was found in a range of 25-50°C. The drug dissolution rate and the matrix diffusional contribution increased with the increased temperature which this soluble drug diffused through the gel rapidly (Ford et al 1985b). Increasing the agitation speed in a dissolution test will generally increase the erosion of an HPMC matrix, especially matrices containing low viscosity HPMC grades which have lower gel strength (Kavanagh & Corrigan 2004).

Surfactants are often added to the dissolution medium in the case of insoluble drugs to increase drug solubility and improve drug wetting characteristics (Maggi et al 1996), however the work in this thesis shows that their presence may also lead to changes in polymer hydration behaviour.

1.5. Organic salts

An organic salt is the reaction product of an organic acid and an inorganic base. Organic acids are compounds containing C, H, O as the major elements, with one or more functional groups which can form acidic salts. For example, maleic acid which has two carboxylic groups may form both neutral and acid salts (maleate), whilst methanesulfonic acid, a strong acid with one sulfonyl group ($-\text{SO}_3\text{H}$), can form stable salts (mesylate) with many weak bases. Some organic acids and their salts exhibit stereochemistry of in which different stereoisomers exhibit different physical properties. Examples of these include tartaric, lactic and malic acids (Stahl 2002).

1.5.1 The applications of organic salts

1.5.1.1 Organic salts used as drugs

Some organic salts are used for a direct therapeutic effect. For example, sodium propionate is used as an antifungal agent (Wade 2000), sodium formate is used in certain external preparations for musculoskeletal and joint disorders (Martindale 2005) and sodium valproate is utilized as an antiepileptic agent (BNF 57, 2009, p.258) Sodium octanoate is used as an adjuvant to stabilize albumin solutions against the effect of heat (Martindale 2005). Organic salts used as therapeutic agents or drug counter-ions, may be developed as HPMC controlled release dosage forms. However their influence on the drug release properties of these matrices is unknown and for this reason, the interaction between organic salts and HPMC should be studied.

1.5.1.2 Organic salts used as drug counter-ions

In pharmaceutical science, organic salts are used as drug counter-ions most commonly in order to improve drug solubility. For instance, mesylate, the salt of methanesulfonic acid, is a frequently used salt form of basic drugs. Salts of some

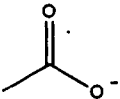
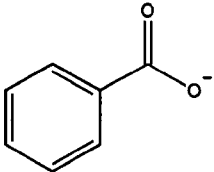
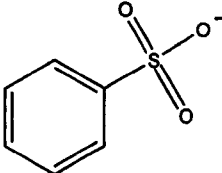
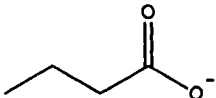
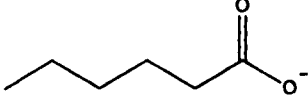
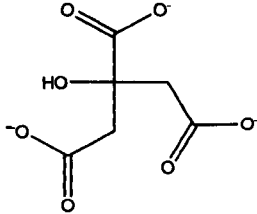
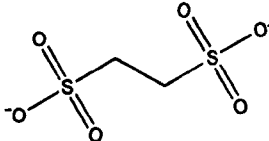
organic bases are also used as counter-ions to acidic drug substances such as triethylamin, diethylamine, piperazine, and trometamol (TRIS) (Stahl 2002).

Typically, stronger anions and cations will be utilised to enable salt formation. For example, salt forms of new chemical entities approved by the FDA from 1995 to 2006 were mostly prepared (>70%) with strong counterions (hydrochloride, hydrobromide/bromide, sulphate/bisulfate, nitrate, sodium, calcium, potassium) (Serajuddin 2007). However, Agharkar and co-workers reported for a basic drug, antimalarial agent α -(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol, that solubility of lactate salt was 200 times as soluble as the hydrochloride salt (Agharkar et al 1976).

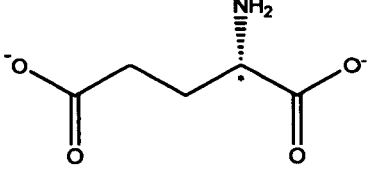
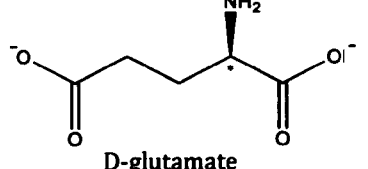
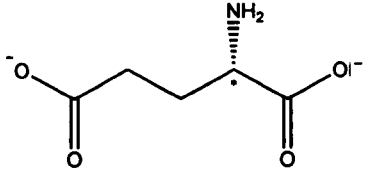
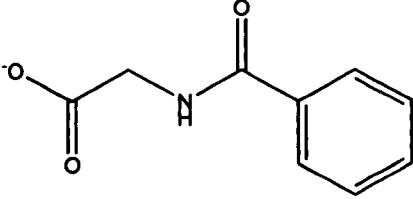
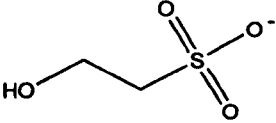
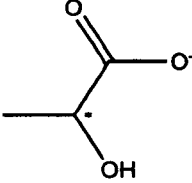
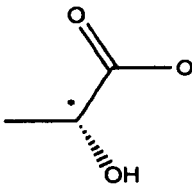
Actually, the principles of salt formation involve various factors including pH-solubility interrelationship, structure-solubility relationship, effects of organic solvent from synthesis or used in parenteral or other liquid dosage forms on salt solubility, effect of counterion on salt solubility, etc. (Serajuddin 2007). Additionally, the pH-modifiers will be used in dosage forms to avoid the conversion of salts to their respective free acid or base forms which may occur upon storage and also due to pH effects in the GI tract.

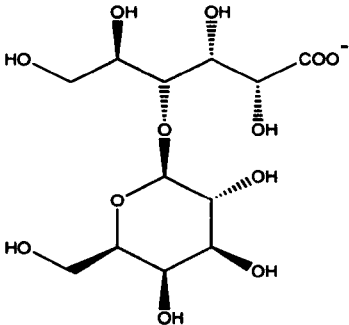
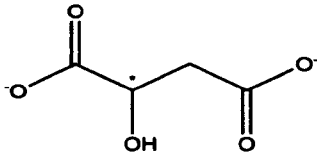
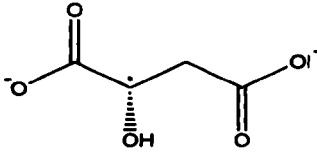
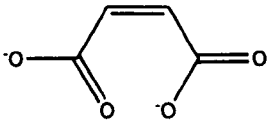
1.5.1.2.1 A survey of the use of organic salts as counter-ions to drugs

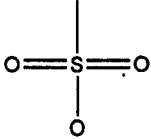
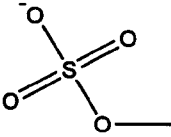
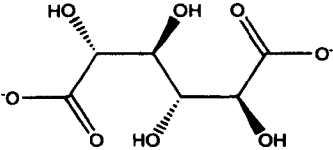
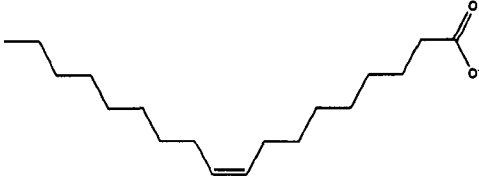
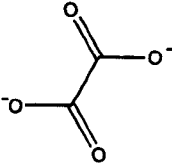
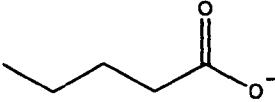
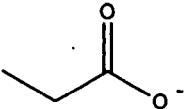
A survey of drug counter-ions was conducted in order to identify organic salts for further investigation. The results of this survey are summarized in Table 1.3.

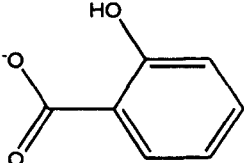
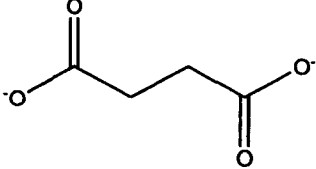
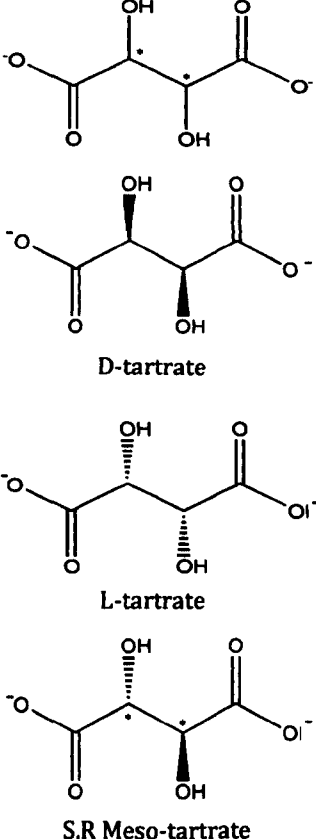
Organic salts	Chemical structure	Examples of drugs utilising this counter-ion
Acidic salts		
Acetate, diacetate		atosiban, cyproterone, flecainide, desmopressin, cetorelix, buserelin, leuprorelin, nafarelin, goserelin, glatiramer, tetracosactide, chlorhexidine, caspofungin
Benzoate		metronidazole, rizatriptan, denatonium
Besilate, besylate, benzenesulfonate		amlodipine, atracurium, cisatracurium, phenbutamide
Butyrate		clobetasone, hydrocortisone
Caproate		hydroxyprogesterone
Citrate		piperazine, clomifene, fentanyl, tamoxifen, toremifene, sildenafil, orphenadrine, ranitidine bismuth citrate, dacarbazine
Edisilate, ethane-1,2-disulfonate		clomethiazole

Organic salts	Chemical structure	Examples of drugs utilising this counter-ion
Embonate, pamoate*		chlorpromazine embonate, triptorelin pamoate
Estolate (Propionate laurylsulfate)		erythromycin estolate
Fumarate, hydrogen fumarate, acid fumarate, difumarate		bisoprolol, ketotifen, ferrous (1:1), formoterol (2:1), tenofovir disoproxil (1:1), quetiapine (2:1), ibutilide, aminorex, bencyclane, clemastine (1:1), ketotifen, emedastine
Gluconate (stereoisomer)		ferrous, calcium, chlorhexidine, quinidine, phenylamine, dexchlorpheniramine, dihydroquinidine

Organic salts	Chemical structure	Examples of drugs utilising this counter-ion
Glutamate (stereoisomer)	  <p>D-glutamate</p>  <p>L-glutamate</p>	Arginine
Hippurate		Methenamine
Isetionate		pentamidine, propamidine, hexamidine
Lactate (stereoisomer)	  <p>D-lactate L-lactate</p>	pentazocine, milrinone, calcium lactate, sodium lactate, ethacridine, amoxicillin, haloperidol, isoxsuprine, trimethoprim, prenylamine

Organic salts	Chemical structure	Examples of drugs utilising this counter-ion
Lactobionate		dobutamine, erythromycin
Malate (stereoisomer)	 <p data-bbox="529 949 628 975">D-malate</p>  <p data-bbox="529 1161 628 1187">L-malate</p>	almotriptan hydrogen malate, pizotifen hydrogen malate
Maleate		azatadine, timolol, enalapril, chlorpheniramine, fluvoxamine, rosiglitazone, ergometrine, levomepromazine, trimipramine, prochlorperazine, methysergide, lisuride, brompheniramine, dimetindene, methyl ergometrine, dexchlorpheniramine, midazolam, mepyramine, nomifensine, perhexiline, pheniramine, pirsudanol, triethylperazine, trimebutine

Organic salts	Chemical structure	Examples of drugs utilising this counter-ion
Mesilate, mesylate, methanesulfonate		doxazosin, desferrioxamine (deferrioxamine), pralidoxime, phentolamine, dolasetron, benztropine, nelfinavir, saquinavir, bromocriptine, quinupristin with dalfopristin (both as mesilate salts, 3:7), imatinib, eprosartan, reboxetine, pergolide
Methylsulphate		neostigmine
Mucate, galactarate		isometheptene
Oleate		ethanolamine
Oxalate		escitalopram, naftidrofuryl
Pentanoate (valerate)		betamethasone, diflucortolone, estradiol, hydrocortisone
Propionate, dipropionate		clobetasol, fluticasone, testosterone, vitamin A, betamethasone

Organic salts	Chemical structure	Examples of drugs utilising this counter-ion
Resinate	A polymeric counter ion which is an ion exchange resin e.g. $C_{19}H_{29}COO^-$	diclofenac (SR), dihydrocodeine (SR)
Salicylate		choline
Succinate, acid succinate, hydrogen succinate		sumatriptan, solifenacin, metoprolol, doxylamine, oxaflumazine, frovatriptan, benfurodil, bamethan, cibenzoline, deanol, ergotamine, loxapine
Tartrate, bitartrate, hydrogen tartrate (stereoisomer)	 <p style="text-align: center;">D-tartrate</p> <p style="text-align: center;">L-tartrate</p> <p style="text-align: center;">S,R Meso-tartrate</p>	metoprolol, dimetacrine, alimemazine, zolpidem, ergotamine, tolterodine, brimonidine, rivastigmine, metaraminol, vinorelbine, epinephrine

Organic salts	Chemical structure	Examples of drugs utilising this counter-ion
Teoclate		promethazine, diphenylpyraline
Xinafoate		salmeterol
Basic salts		
Diethylamine, diethylammonium		diclofenac
Edetate		dicobalt, sodium calcium edetate, disodium edentate
Erbumine		perindopril
Trometamol, tromethamine, TRIS		carboprost, fosfomycin, ketorolac, lodoxamide, desglugastrin, dexketoprofen, iloprost

Table 1.3 Organic species currently used as drug counter-ions (references: Stahl 2002; BNF 57; USP 2006; Martindale 2005; Merck Index 2006)

1.5.2 Hofmeister effect

More than a hundred years ago, in 1888 Lewith and Hofmeister published accounts describing wide differences between the minimum concentrations of neutral salts required to precipitate a protein from solution. Since then, there has been a steady stream of studies and supporting data, expanding the scope from simple protein solubility, to a broad range of other phenomena involving biological macromolecules that take place in the presence of salts and other small molecules. The Hofmeister effect describes the phenomenon in which the solubilities of macromolecules (such as proteins, enzymes, and polymers) are modulated by salts (Baldwin 1996; Cacace et al 1997; Cho et al 2006; Zhang and Cremer 2006; Giner et al 2007; Liu et al 2008; Tóth et al 2008).

Salts have been classified according to their ability to alter water structure. Ions that enhance the hydrogen bond structure of water, reduce the solubilities of hydrophobic side groups and tend to cause 'salting out'. These are known as kosmotropes or water-structure makers. In contrast, ions that loosen hydrogen bond structure, increase non-polar solubilities and tend to cause 'salting in' of molecules. These are known as chaotropes or water-structure breakers. Kosmotropes are normally small ions with high charge densities such as Cl^- . These ions tend to succeed in competing for water molecules with polymer chains, decrease the number of free water molecules in the polymer hydration sheath, and can facilitate hydrophobic associations. In the case of HPMC this results in a decrease of the thermogelation temperature. The salting-in salts, which normally are large anions with low charge densities such as I^- . These function as water-structure breakers and enhance the solubility of polymers (Cacace et al 1997; Cho et al 2006; Koga et al 2006; López-León et al 2007; Nucci & Vanderkooi 2008; Yang 2009). Recent studies have found that bulk water structure is not central to the Hofmeister effect, and models are being developed that describe direct ion-macromolecule interactions as well as interactions with water molecules in the hydration sheath of macromolecules. For example, in PNIPAM solution anions have been found to exhibit direct interactions with macromolecules and their immediately adjacent hydration sheath by (i) direct hydrogen bonding with amide

moieties (ii) increasing the cost of hydrophobic hydration (i.e. by raising the surface tension of the polymer/water interface), leading to salting-out of the polymer, and (iii) direct binding to the side chain amide moieties, leading to salting-in of the polymer (Zhang et al 2005; Zhang & Cremer 2006). Liu et al (2008) have studied the effect of a range of inorganic salts and isotropic solvents on the thermogelation behavior of HPMC in aqueous solutions, and found that to decrease the sol:gel transition temperature of HPMC by influencing the structure of water. The thermodynamics HPMC of gelation was determined by the salt types and concentration.

1.6. Surfactants

1.6.1 The Solution Properties of Surfactants

Surfactants are amphiphiles which possess both hydrophilic (polar headgroup) and hydrophobic (non-polar tail) domains (Figure 1.6). They can be anionic, cationic, zwitterionic, or nonionic depending on their hydrophilic head group. At an appropriate concentration (the critical micelle concentration or cmc) surfactants can associate into regular structures called 'micelles'. In a hydrophilic solvent such as water, the important characteristic of micelles is that hydrocarbon chains (hydrophobic tails) constitute the inner part or core of the micelle whereas the polar headgroups are positioned in a thin layer at the surface of the micelle.

Figure 1.6 shows the generalised structure of a micelle in water. The geometric form will depend on the surfactant concentration and the type and concentration of any additives present. The presence of salts results in the structural transition of micelles (Siddiqui et al 2001). In general, micelles are spherical at surfactant concentrations ranging from the cmc to at least ten times the cmc. At higher surfactant concentrations or in the presence of additives, rod-like micelles will form. At very high surfactant concentrations or with large amounts of additives present, liquid crystalline phases occur in which surfactant starts to separate out of solution with in most cases, a hexagonal or lamellar phase in phase equilibrium with the aqueous micellar phase (Florence & Attwood 2009).

The solubilising power of micelles is associated with the hydrocarbon core. Non-polar molecules generally solubilise in the core region of micelle, although simple geometry shows that parts of the solubilised molecule will be close to the headgroup region (Lindman 2002a; Birdi 2003).

Moreover, many industrial applications use more than one surfactant to obtain the preferable effects. Mixed micelles can be (i) surfactant mixtures with no net interaction (similar head group, but different chain lengths) e.g. a mixture of SDS with a nonylphenol with 10 moles ethylene oxide (NP-E₁₀) (ii) surfactant mixtures with a net interaction between for example anionics and nonionics (which shield

the repulsion of negative charges), or anionics and cationics (in which a strong interaction occurs between opposite charges) (Tadros 2005).

Figure 1.7 diagrammatically represents the concentration dependence of some physico-chemical properties of micelle-forming surfactant solutions. At low concentrations, most properties (except for the surface tension which rapidly decreases with surfactant concentration) are similar to those of simple electrolytes. At higher concentrations (above the cmc), surface tension and osmotic pressure take on an approximately constant value, while the propensity for light scattering increases and molecular self-diffusion decreases. All these observations suggest a change-over from a solution containing single surfactant molecules to self-assembled or self-associated structures (Lindman 2002a; Tadros 2005; Florence & Attwood 2009).

1.6.2 Surfactant-Polymer Systems

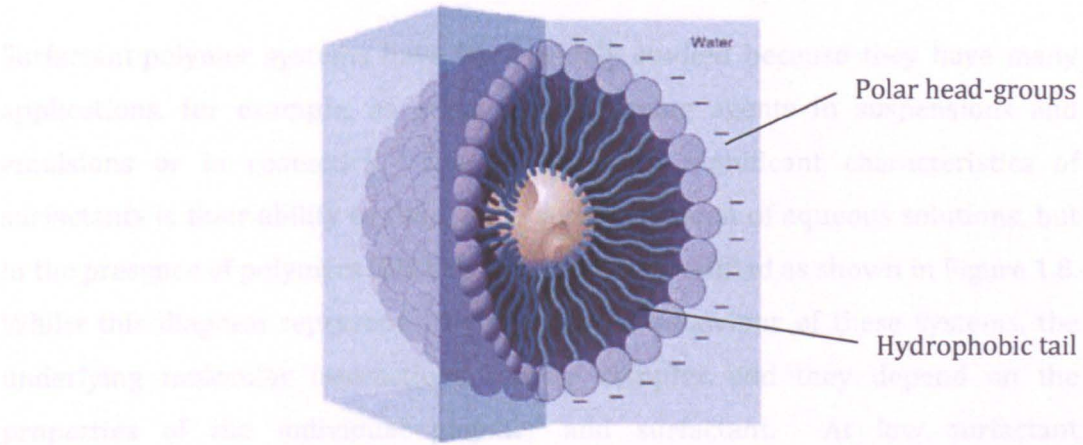


Figure 1.6 Generalised structure of a surfactant micelle in water. (Adapted from Muller 2004)

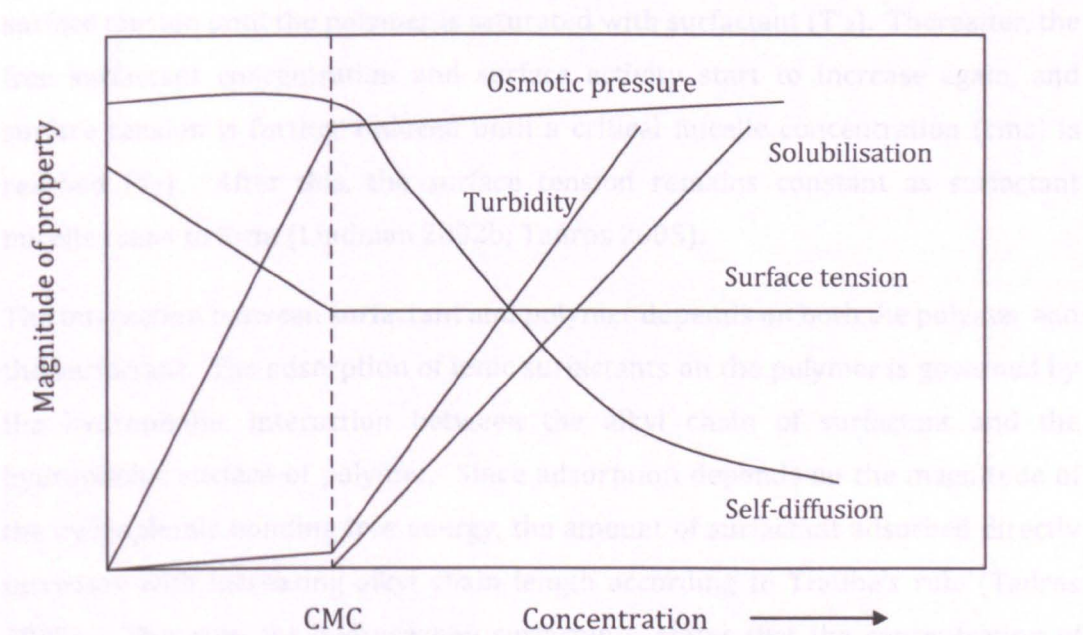


Figure 1.7 Schematic representation of the concentration dependence of some physical properties for solutions of micelle-forming surfactants. (Adapted from Lindman 2002a; Tadros 2005 and Florence & Attwood 2009)

1.6.2 Surfactant-Polymer Systems

Surfactant:polymer systems have been widely studied because they have many applications, for example, as enhanced thickening agents in suspensions and emulsions or in cosmetics. One of the most significant characteristics of surfactants is their ability to reduce the surface tension of aqueous solutions, but in the presence of polymers this behaviour can be modified as shown in Figure 1.8. Whilst this diagram represents the generalized behaviour of these systems, the underlying molecular interactions can be complex and they depend on the properties of the individual polymer and surfactant. At low surfactant concentrations, there may or may not be a lowering of surface tension, depending on the surface activity of polymer. At a certain critical concentration (the so-called 'critical association concentration', 'critical aggregation concentration' or CAC), there is an onset of surfactant-polymer association. Above this concentration, there is no further increase in surfactant activity and thus no further reduction of surface tension until the polymer is saturated with surfactant (T'_2). Thereafter, the free surfactant concentration and surface activity start to increase again, and surface tension is further reduced until a critical micelle concentration (cmc) is reached (T_2). After this, the surface tension remains constant as surfactant micelles start to form (Lindman 2002b; Tadros 2005).

The interaction between surfactant and polymer depends on both the polymer and the surfactant. The adsorption of ionic surfactants on the polymer is governed by the hydrophobic interaction between the alkyl chain of surfactant and the hydrophobic surface of polymer. Since adsorption depends on the magnitude of the hydrophobic bonding free energy, the amount of surfactant adsorbed directly increases with increasing alkyl chain length according to Traube's rule (Tadros 2005). This rule, for hydrocarbon surfactants, states that the concentration of surfactant at which a given reduction of surface tension is observed, decreases in a regular progression with each $-CH_2-$ unit in the homologous series (Krishnan et al 2003, Pinheiro et al 2004).

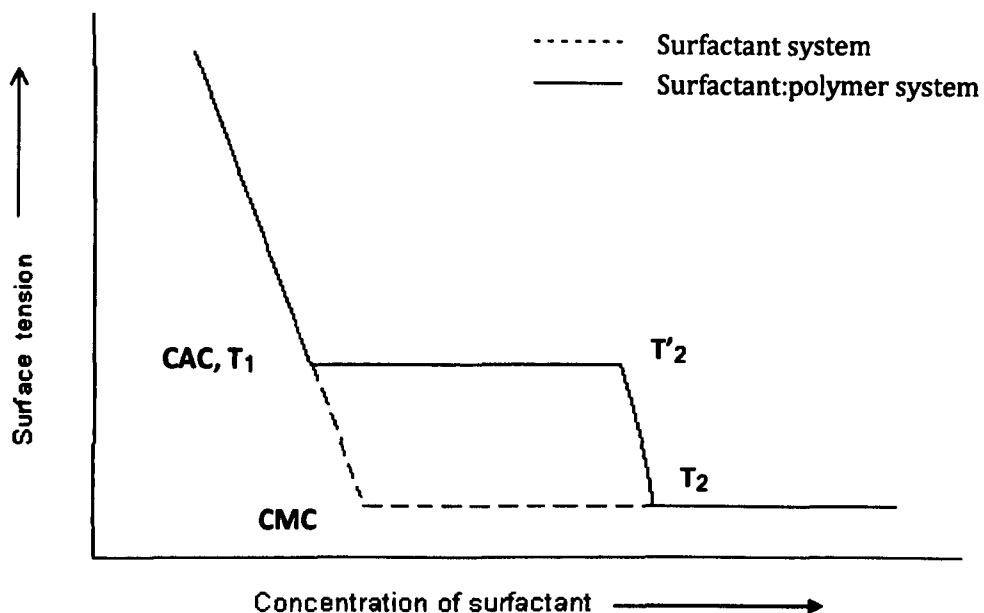


Figure 1.8 Schematic plot of the surface tension of surfactant solutions as a function of surfactant concentration in the presence of polymer. CAC = critical aggregation concentration, cmc = critical micelle concentration, T_1 = the onset point of CAC, T'_2 = the saturated point of polymer:surfactant association, T_2 = the cmc reached point. (Adapted from Lindman 2002b)

There are many factors which can influence the association between surfactants and polymers and these include (i) temperature (ii) addition of electrolyte (iii) surfactant chain length (iv) surfactant structure (v) surfactant classes (vi) polymer molecular weight (vii) amount of polymer (viii) polymer structure and hydrophobicity.

Surfactant:polymer systems that exhibit this behaviour include ionic surfactants and uncharged polymers, and examples include SDS:poly(vinylpyrrolidone) (PVP), SDS:PEO, (anionic or cationic) surfactant: poly(vinyl alcohol), PEO, PVP, or MC (Goddard 1990; Goddard 1993).

There are also other types of surfactant:polymer interaction, for example, (i) surfactants and hydrophobically modified polymers which results in an association structure e.g. SDS:HM-HEC (or hydrophobically modified hydroxylethyl cellulose), (ii) surfactants and polyelectrolytes which are opposite-charged polymers and results in an strong intermolecular association e.g. SDS:cationically modified cellulosic polymer (or Polymer JR, Union Carbide), cationic surfactants:anionic polyelectrolytes.

1.6.3 Surfactants in Pharmaceutical applications

Surfactants are widely used in pharmaceutical applications. They are used as solubilising agents for poor solubility drugs, as wetting agents, and as emulsifying agents. Common surfactants which are used in pharmaceutical applications are summarized in Table 1.4, and from this list we chose the alkyl sulphates as the most appropriate for our study.

Surfactants	Principal Application	Concentration used (%)	Form
Anionic			
Docusate sodium (Dioctyl sodium sulfosuccinate)	Mainly used in capsule and tablet formulations as a wetting agent; also used in laxatives	0.01-1.0	Solid
Emulsifying wax BP (Cetostearyl alcohol and sodium lauryl sulphate)	Emulsifying agent in cosmetics and topical pharmaceutical formulations	3-30	Wax
Lecithin (Phospholipids)	Emulsifying agent; solubilising agent; emollient	0.25-10	Viscous liquid to semisolid
Sodium lauryl sulfate (SLS or SDS)	Emulsifying agent; detergent in medicated shampoos; skin cleanser in topical application; solubilising agent; tablet lubricant; wetting agent	0.5-10 (external use, >0.0025, 1-2 (internal use)	Solid
Cationic			
Benzalkonium chloride	Antimicrobial preservative; antiseptic; disinfectant; solubilizing agent; wetting agent	0.01-0.02	Solid
Benzethonium chloride	Antimicrobial preservative; wetting agent; solubilising agent; topical disinfectant	Up to 0.5%w/v	Solid
Cetrimide	Antimicrobial preservative; topical antiseptic; cleanser and disinfectant	0.005; 0.1-1.0	Solid
Nonionic			
Glyceryl monostearate	Emulsifying agent; solubilizing agent; stabilizing agent; emollient; sustained-release ingredient; tablet and capsule lubricant	HLB value: 3.8	Wax-like solid

Surfactants	Principal Application	Concentration used (%)	Form
Nonemulsifying glyceryl monooleate	Used in topical formulations as an emollient and emulsifier (water-in-oil emulsions); stabilizer (oil-in-water emulsions)	HLB value: 3.3	Oily liquid or paste
Poloxamer	Dispersing agent; emulsifying and coemulsifying agent; solubilizing agent; tablet lubricant; wetting agent	0.3-50 Depend on the usage	Liquid or solid
Polyethylene glycol (PEG, Macrogol)	Ointment, suppository base; suspending agent; co-emulsifier; tablet binder; plasticizer; tablet and capsule lubricant; used in film coating of tablets.	>5% w/w of high molecular weight PEG for tablet binders; 10-15% w/w PEG 6000 for thermoplastic granulations; 30% v/v PEG 300, PEG 400 for parenteral dosage forms	Liquid grades (PEG 200-600), solid grades (PEG>1000)
Polyoxyethylene alkyl ethers (Cetomacrogol, Brij)	Emulsifying agent; solubilizing agent; wetting agent; gelling and foaming agents	Depend on the usage e.g. 15-20 (gelling agents)	Liquid, paste, or solid
Polyoxyethylene castor oil derivatives (Cremophor)	Emulsifying agent; solubilizing agent; wetting agent; used in oral, topical, and parenteral pharmaceutical formulations	HLB value: 12-17 (depend on grade); 1 mL of a 25% v/v aqueous Cremophor RH 40 or Cremophor EL for solubilizing vitamins or certain drugs	Liquid or paste
Polyoxyethylene stearate	Emulsifying agent; solubilizing agent; wetting agent	0.5-10	Solid or paste

Surfactants	Principal Application	Concentration used (%)	Form
Polysorbate (Tween)	Emulsifying agent; solubilising agent; wetting agent; dispersing/suspending agent	1-15	Oily liquid, liquid or solid
Sorbitan esters (Span)	Emulsifying agent; solubilising agent; wetting agent; dispersing/suspending agent.	1-15	Liquid or solid

Table 1.4 Surfactants commonly used in Pharmaceutical applications (as listed in the Handbook of Pharmaceutical Excipients 2000)

1.7. Aims and objectives of PhD

1.7.1 Principal aims

The overall aims of this thesis was to (i) investigate the influence of soluble organic acid salts on the properties of HPMC solutions and the release performance of HPMC matrices (ii) to identify (within the limited range investigated) any structure-activity relationships and (iii) if these effects were significant to propose a mechanism of interaction between these compounds and HPMC. These salts are often the forgotten components of matrix formulations because they are present simply as drug counter-ions. However, previous work on soluble amino acids had suggested they may have effects on HPMC solution and matrix behaviour. The understanding that these effects were related to alkyl chain length, lead to a further investigation involving a homologous series of alkyl sulphate surfactants, and a short study to investigate if sodium dodecyl sulphate might be used to recover failing HPMC formulations. The knowledge gained from this study might provide the basis for rational selection of salt forms for incorporation into HPMC formulations, and perhaps the use of organic salts to obtain a desired drug release rate.

To accomplish these aims, the thesis is divided into the following experimental chapters:

Chapter 3: The effect of organic drug counter-ion salts, on the properties of HPMC solutions, and the investigation of the mechanism of interaction between these organic salts and HPMC.

Chapter 4: The effect of organic salts on the drug release performance of HPMC matrices, and the structure-activity relationships of their effects.

Chapter 5: The effect of a homologous series of alkyl sulphate surfactants on the properties of HPMC solutions and drug release performance of HPMC matrices, and the mechanism of interaction between these surfactants and HPMC.

Chapter 6: Can HPMC matrices be recovered using incorporated sodium dodecyl sulphate?

I hope that this work might provide a better understanding of the influence of the organic salts and surfactants which may be incorporated into HPMC matrix tablets, so that the appropriate consideration can be given to their effects when designing formulations to achieve a desired extended release rate.

Chapter 2

Materials and General Methods

2.1 Materials

2.1.1 Hydroxypropyl methylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) USP Type 2910 (Methocel™ E4M CR Premium EP/USP) and USP Type 2208 (Methocel™ K4M CR Premium EP/USP) were a kind gift from Colorcon Ltd, Dartford, UK. The E4M batch (QF11012N03) contained 8.6% hydroxypropyl and 29.3% methoxyl substitution and was used as the principal HPMC throughout this thesis. The K4M batch (TD09012N11) contained 8.4% hydroxypropyl and 23.3% methoxyl substitution and was used in some studies. These batches were typical of USP 2910 and USP 2208 HPMCs. The detail of grades and batches are also shown in Appendix 1. The moisture content was monitored at intervals using a MB45 Moisture Analyser (Ohaus Corporation, New Jersey, USA) and remained steady at 3% w/w. Results are shown in Appendix 2. This is within recommended working limits (Doelker 1993).

2.1.2 Other materials

Comprehensive details of all other materials, including the organic salts, organic acids, surfactants, tablet excipients, other reagents and the water used throughout this study can be found in Appendix 1.

2.2 Methods

2.2.1 The preparation of HPMC solutions

2.2.1.1 10% w/w HPMC stock solutions

Concentrated stock solutions containing 10% w/w HPMC were prepared using the hot/cold dispersion method for cellulose ethers (Dow Chemical Company 2002b). The required amount of HPMC was dispersed in water which had been pre-heated to $>80^{\circ}\text{C}$ using a bench-top magnetic-stirrer with a hot plate (RCT basic, IKA Labortechnik Staufen, Janke&Kunkel GMBH&CO.KG, Germany). The dispersion was then put into ice and cooled to room temperature while stirring was continued using a bench-top magnetic stirrer (KMO2 basic, IKA® Labortechnik GMBH&CO.KG, Germany). The solution was then stored at $2-8^{\circ}\text{C}$ for at least 24 hours prior to use.

2.2.1.2 1-2% w/w HPMC stock solutions

Solutions containing 1-2% w/w HPMC were prepared by mixing the required weight of 10% w/w HPMC stock solution with water and making up to volume. Solutions were stoppered, stirred overnight and stored at $2-8^{\circ}\text{C}$ for at least 24 hours prior to use.

2.2.2 The preparation of 0.1% and 1% w/w HPMC solutions containing additives

HPMC stock solutions, and solutions of additives (e.g. drugs, salts and surfactants) were prepared separately to avoid any interactions prior to complete dissolution or hydration. The required amount of each additive was dissolved in water of about nine tenths of the final weight before being incorporated into a 1%w/w HPMC stock solution one tenth of the final weight to obtain solutions containing additives in 0.1%w/w HPMC. The mixtures were covered, stirred until homogeneous, and stored at $2-8^{\circ}\text{C}$ for at least 24 hours prior to use.

2.2.3 Turbidimetric determination of HPMC cloud point temperature

HPMC solutions undergo a thermoreversible sol:gel transition on heating and cooling (as described in Chapter 1 Section 1.3.1) and the temperature at which this occurs can be determined by turbidimetric, light scattering, rheological or calorimetric methods (Ford 1999). This temperature provides a sensitive measure with which to compare the molecular hydration of the polymer in solution in the presence of various additives. The significance of the sol:gel transition temperature (SGTT) is discussed in more detail in Chapter 1 Section 1.3.1. In this study the SGTT of HPMC solutions was measured by cloud point measurements using a multicell, temperature-ramped, white light turbidimeter (Cloud point apparatus, Medical Physics, Queen Medical Centre NHS trust, Nottingham, UK). This instrument detects the light transmission through sample solutions as a function of temperature, and detects the growth of aggregated polymer which behave as point scatterers of visible light (Kratohvil 1987; Chu 1991).

2.2.3.1 Operational method

A schematic diagram illustrating the operation of the cloud point apparatus is shown in Figure 2.1. The experimental method and the operation of the apparatus will be described together, as follows:

- Sample solutions were filled into a cuvette (10 mm pathlength, quartz cuvette, Starna companies, U.K.) carefully avoiding bubbles which can affect the light scattering.
- Sample cuvettes were placed in the temperature-controlled block as shown in Figure 2.1.
- Before the test started, the baseline of each sample was investigated by running a light beam through the blank.
- During the test, sample solutions were heated in the temperature controlled block by a water thermocirculator (the temperature-ramp was set at a rate of $1.5^{\circ}\text{C min}^{-1}$), and stirred continuously using a custom made magnetic stirrer (Medical Physics, Queen Medical Centre NHS trust, Nottingham, UK) to ensure uniform temperature distribution and

homogeneity. The temperature of the sample was controlled by the surrounding heated block, and the temperature of the sample monitored by TC-08 silicone-coated thermocouples (Pico technology Ltd, Cambridge, UK). These were placed carefully in the sample cells as close as possible to the light beam but ensuring that the probe did not impede the path of the light beam or was in contact the side of the cuvette.

- A beam of white light passes through the sample cell, and the intensity of transmitted light through the sample was detected by the photodiode. A PC interface converted the signals and graphs on the screen displayed how light transmission changed as a function of temperature. The temperatures at which light transmittance is reduced to 50% is termed the cloud point temperature (CPT) and this represented SGT_T (Sarkar 1979).

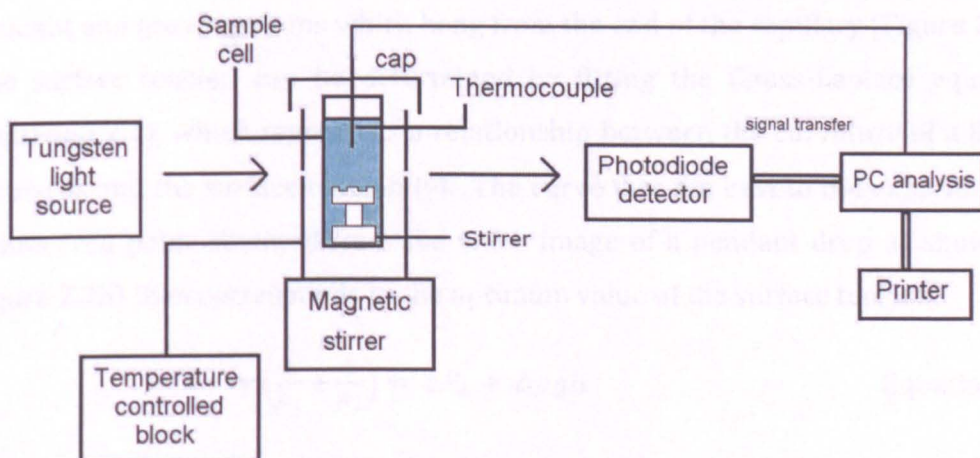


Figure 2.1 Schematic diagram of the cloud point temperature apparatus.

2.2.4 Tensiometric determinations of HPMC surface tension

HPMC possesses surface activity, as described in Chapter 1 Section 1.3.3. The surface activity of solutions can be determined by tensiometry and goniometry by various methods including the Du Noüy Ring, Wilhelmy plate, spinning drop, pendant drop, sessile drop, bubble pressure, drop (weight) volume and capillary rise methods (Mulqueen & Huibers 2002; Goodwin 2004; Tadros 2005). The significance of surface tension in polymer-surfactant interactions are discussed in more detail in Chapter 1 Section 1.3.3 and 1.8.3. In this study, the surface tension was measured by using pendant drop method using a Profile Analysis Tensiometer (Sinterface tensiometer PAT1, Berlin, Germany).

2.2.4.1 Measuring surface tension using a profile analysis tensiometer

The Profile Analysis Tensiometer consists of a dosing system with a capillary (from which to generate a drop), a video camera with an objective, and a frame grabber to transfer the image into a PC. This tensiometer can measure both the surface and interfacial tensions of liquids based on the analysis of the shape of pendant and growing drops which hang from the end of the capillary (Figure 2.2a). The surface tension can be determined by fitting the Gauss-Laplace equation (Equation 2.1), which represents a relationship between the curvature of a liquid meniscus and the surface tension (γ). The curve that fits best to the experimental points (red point obtained from the video image of a pendant drop as shown in Figure 2.2b) then corresponds to the optimum value of the surface tension.

$$\gamma \left(\frac{1}{R_1} + \frac{1}{R_2} \right) = \Delta P_0 + \Delta \rho g h \quad \text{Equation 2.1}$$

Where γ is the surface tension, R_1 and R_2 are the main radii of curvature, ΔP_0 is the pressure difference in a reference plane, $\Delta \rho$ is the density difference, g is the acceleration due to gravity, and h is the vertical height of the drop measured from the reference plane.

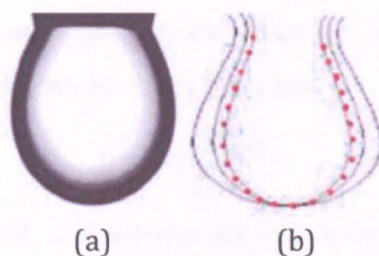


Figure 2.2 (a) a pendant drop of liquid (b) the liquid meniscus used for the Gauss-Laplace calculation

2.2.4.2 Surface tension measurements of HPMC solutions

Surface tension measurements were conducted by pendant drop using the Profile Analysis Tensiometer (Sinterface tensiometer PAT1, Berlin, Germany) on 0.1 % w/w HPMC solutions containing surfactants or organic salts at 20 ± 1 °C. Replicate measurements were automatically conducted 100 times on each sample. The relative standard deviations of the 100 measurements were smaller than 0.05%. Three separate aliquots of each solution were measured in this way.

2.2.5 Density measurement

Prior to conducting the surface tension measurements, the density of the sample solution was measured. Density values for 0.1 % w/w HPMC solutions containing surfactants or organic salts were obtained using a DMA 5000 oscillating U-tube Density Meter (Anton Paar, Graz, Austria). The measurement cell comprises a borosilicate glass U-shaped tube inside a thermostat jacket. The U-shaped tube sensor filled with ~1mL of sample was electronically excited to simultaneously oscillate at its fundamental resonant frequency and its harmonics. The oscillation characteristics are then measured with an integrated reference oscillator positioned in close thermal contact with the U-shaped tube. If the sample volume trapped between the oscillation nodes is assumed to be constant, the oscillation frequency is a function of sample density. The density determination is based on measuring the period of oscillation of a vibrating U-shaped tube filled with sample, and using a relationship between the period of oscillation and the density (Equation 2.2) which holds as long as the sample is not too viscous (Fitzgerald

2000). Mean density values ($n=3$) were obtained at $20\pm1^\circ\text{C}$ and were used subsequently in the surface tension measurements.

$$\tau = 2\pi \sqrt{\frac{\rho v + m}{c}} \quad \text{Equation 2.2}$$

Where τ is oscillation period, ρ is sample density, v is cell volume, m is cell mass and c is spring constant.

2.2.6 Rheological determinations

2.2.6.1 Rheology, viscosimetry and viscoelasticity

Viscosimetry, a branch of rheology, is an easy accessible but significant analytical method for the characterization of polymers in solution. Viscosimetry allows for a fast and low-priced determination of relevant parameters such as solution structure, volume fraction, coil dimensions, molar mass, viscosity or thermodynamical properties of a polymer in solution (Kulicke & Clasen 2004).

Rheology is the science of deformation and flow which all forms of shear behaviour are described in terms of the behaviour of an ideal viscous liquid and an ideal elastic solid. A force applied to an ideal liquid causes a flow which is termed viscous behaviour whereas the same force applied to an ideal solid causes a deformation which is instantaneously reversed on the removal of the force and is termed elastic behaviour. The behaviour of many real materials is based on a combination of both the viscous and the elastic portion, and they are therefore called viscoelastic (or Maxwell) materials (Barnes et al 1989; Mezger 2006).

HPMC solutions are viscoelastic liquids whose behaviour can be illustrated using the Maxwell model. Figure 2.3 shows the Maxwell model which consists of a spring representing the solid/elastic component (E) and a dashpot representing the liquid/viscous component (V). Initially, when a force (F) is applied (Figure 2.3b), only the spring shows an immediate deformation until a constant deflection value is reached. When the constant force is continuously applied, the piston of the dashpot moves for as long as the force is applied (Figure 2.3c). After a certain period of time, both components show a certain extent of deformation which

corresponds to the degree of the force. When the force is removed, the spring relaxes immediately and completely to its original state whereas the dashpot does not (Figure 2.3d). The sample is now partly deformed and this deformation corresponds only to the viscous component. The time which a deformed material attempts to return to rest after applying a force strain is known as the relaxation time, and for viscoelastic materials, relaxation occurs at an exponential rate. The relaxation times of polymer solutions depend on the polymer structure and molar mass. Cross-linked polymers possess greater elastic behaviour and show the longer relaxation times whereas non-linked polymers, which may be less entangled (perhaps more hydrated) show more rapid and complete relaxation. The materials with a high molar mass generally show longer relaxation times (Clasen & Kulicke 2001; Mezger 2006).

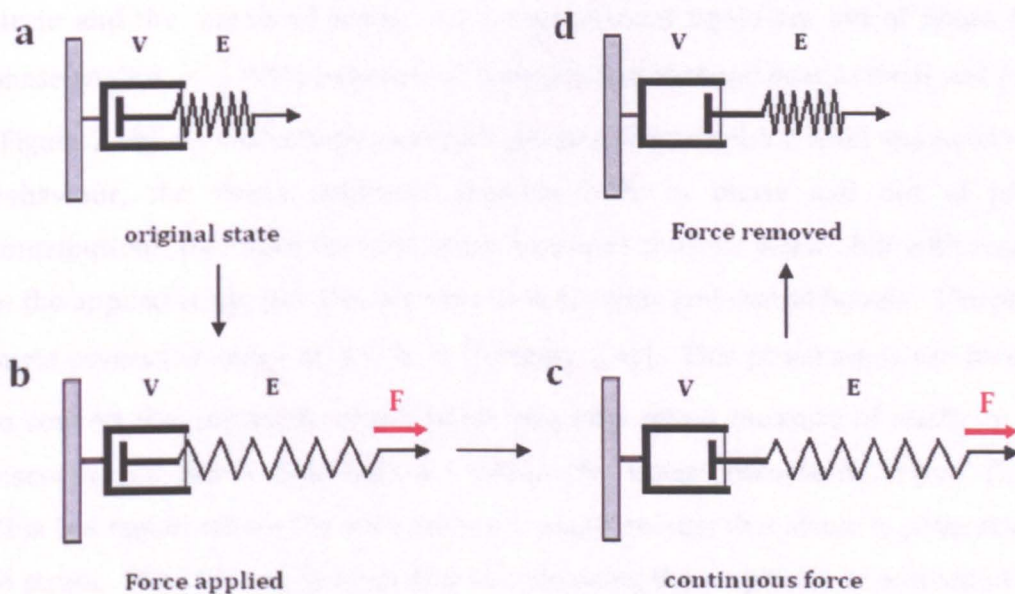


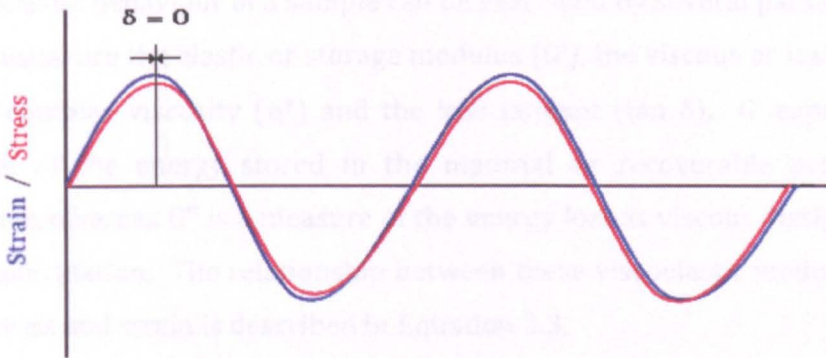
Figure 2.3 Schematic diagram of a single Maxwell model illustrating the deformation of a viscoelastic sample on application of a force. (a) The original state of the sample. (b) Force, F applied (see arrow) causes the spring to extend (deform). (c) The continued force is transferred to piston in the dashpot. (d) Force is removed and the spring returns to its original state while the dashpot does not (deformation is maintained). Adapted from Mezger (2006).

2.2.6.2 Dynamic oscillatory rheology

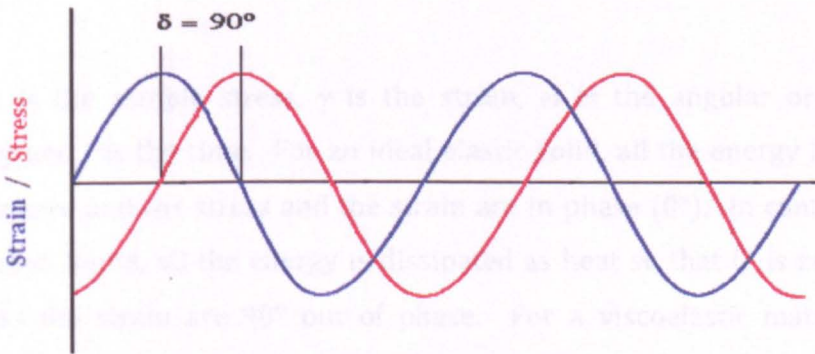
The viscoelastic behaviour of materials can be evaluated by oscillatory (dynamic shear), creep and relaxation tests (Mezger 2006; Rao 2007) and the behaviour of HPMC solutions and HPMC solutions containing organic salts in this thesis has been determined by oscillatory rheology.

The basic principle of oscillatory rheology or dynamic mechanical analysis is to induce a sinusoidal shear deformation in the sample, using a parallel plate or cone and plate geometry, and then measure the sinusoidal stress response. The time scale is determined by the oscillatory or angular frequency (ω) of the shear deformation and the sinusoidal stress and strain relationship depends on the properties of a material. The stress of an ideal elastic solid is exactly in phase with the applied sinusoidal strain deformation as energy applied is stored and then completely returned on sample relaxation (Figure 2.4a). In contrast, the applied strain and the measured stress of a purely viscous liquid are out of phase by a phase angle $\delta = \frac{\pi}{2}$ (90°) because the energy is lost through heat as the liquid flows (Figure 2.4b). In viscoelastic materials because they combine solid and liquid-like behaviour, the stress response contains both in phase and out of phase contributions, therefore the total stress response shows a phase shift with respect to the applied strain that lies between that of solids and that of liquids. The phase angle covers the range of $0 < \delta < \frac{\pi}{2}$ (Figure 2.4c). This phase angle can be used to convert the amplitude of the stress response into a measure of elasticity and viscosity, but this is only accurate within the 'linear viscoelastic region' (LVR). This is a region where the deformation is small enough that stress is proportional to strain. The LVR can be identified by increasing the amplitude of oscillation and noting the magnitude of phase shift and the amplitude ratio. The limit of linearity can be detected when dynamic rheological properties change rapidly from their otherwise almost constant values (Mezger 2006; Rao 2007; Wyss et al 2007).

a) Elastic solid



b) Viscous liquid



c) Viscoelastic material

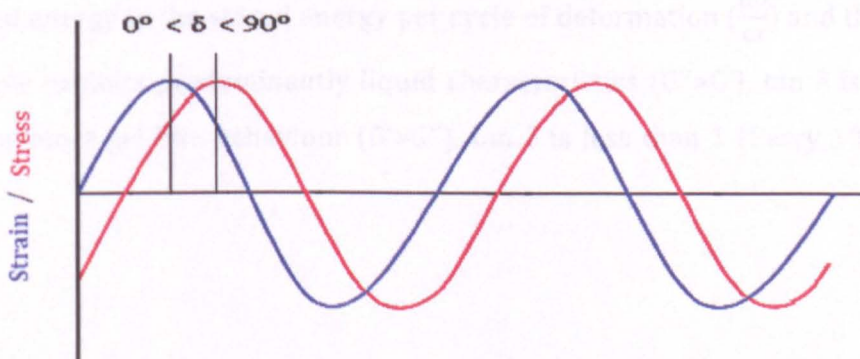


Figure 2.4 Schematic stress response to oscillatory strain deformation for (a) a purely elastic solid, (b) a purely viscous liquid and (c) a viscoelastic material. Adapted from Mezger (2006) and Wyss et al (2007)

2.2.6.3 Descriptive factors used in oscillatory rheology

The viscoelastic behaviour of a sample can be described by several parameters but the most usual are the elastic or storage modulus (G'), the viscous or loss modulus (G''), the complex viscosity (η^*) and the loss tangent ($\tan \delta$). G' expresses the magnitude of the energy stored in the material or recoverable per cycle of deformation whereas G'' is a measure of the energy lost as viscous dissipation per cycle of deformation. The relationship between these viscoelastic moduli, and the sample stress and strain is described in Equation 2.3.

$$\sigma = G''\gamma \sin(\omega t) + G'\gamma \cos(\omega t) \quad \text{Equation 2.3}$$

where σ is the sample stress, γ is the strain, ω is the angular or oscillation frequency and t is the time. For an ideal elastic solid, all the energy is stored so that G'' is zero and the stress and the strain are in phase (0°). In contrast, for an ideal viscous liquid, all the energy is dissipated as heat so that G' is zero and the stress and the strain are 90° out of phase. For a viscoelastic material which possesses both elastic and viscous portions, if G' is much greater than G'' , the material will exhibit more solid-like behaviour. However, if G'' is much greater than G' , the material behaviour is more liquid-like. $\tan \delta$ is the ratio of the dissipated energy to the stored energy per cycle of deformation ($\frac{G''}{G'}$) and therefore if a sample exhibits predominantly liquid characteristics ($G'' > G'$), $\tan \delta$ is greater than 1, or more gel-like behaviour ($G' > G''$), $\tan \delta$ is less than 1 (Ferry 1980; Rao 2007).

2.2.6.4 Operational method

In this thesis, the viscoelastic properties of HPMC solutions and HPMC solutions containing the selected organic salts were determined by using an MCR-301 Rheometer equipped with Rheoplus software (Anton Paar, Graz, Austria). A parallel plate (PP) geometry (2°/50 mm) was used with a gap of 1000 μ m (Figure 2.5). A freshly prepared sample was applied carefully to the peltier temperature-controlled plate using a plastic pipette to avoid air bubbles. When the geometry was lowered to the “trim position”, the excess sample was removed from the edges of the plate using a spatula. The gap was then lowered to 1000 μ m to start the test. A plastic cover with a solvent trap was placed and the sample edge was coated with low-viscosity silicone oil (Fisher Scientific, Leicestershire, UK) to limit sample evaporation.

a) Amplitude sweeps

An amplitude test was undertaken to determine the dependence of G' and G'' on sample strain and to identify the “linear viscoelastic region” (LVR) of each sample. Samples were subjected to increasing strain from 0.01% to 100% using 25 points on a logarithmic scale and at a constant frequency (0.5Hz). The sample temperature was kept constant at $20 \pm 0.1^\circ\text{C}$ during each amplitude sweep. A strain of 1%, within the LVR, was selected for use throughout the study. Results are shown in Figure 2.6.

b) Frequency sweeps

Frequency sweeps were conducted over the range 0.01Hz to 10 Hz using 22 points on a logarithmic scale at a constant strain of 1%. The sample temperature was $20 \pm 0.1^\circ\text{C}$. Measurements were made in triplicate.

c) Temperature sweeps

Temperature sweeps were performed over the range of 20 - 80 $^\circ\text{C}$ at a heating rate of 1°C min^{-1} . Prior experiments undertaken using different rates of heating had established this as an optimum heating rate. Tests were carried out at a constant strain (1%), and frequency (0.5Hz). Measurements were made in triplicate.

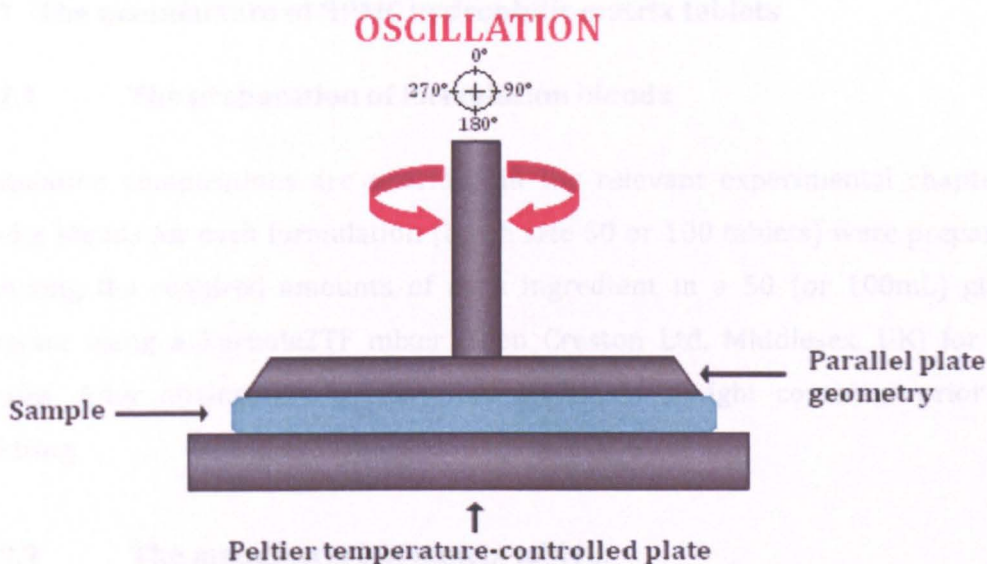


Figure 2.5 Schematic diagram illustrating the parallel plate (PP 2°/50mm) geometry used for rheological determinations of HPMC solutions. The gap between the sample and the PP geometry was 1000 μ m.

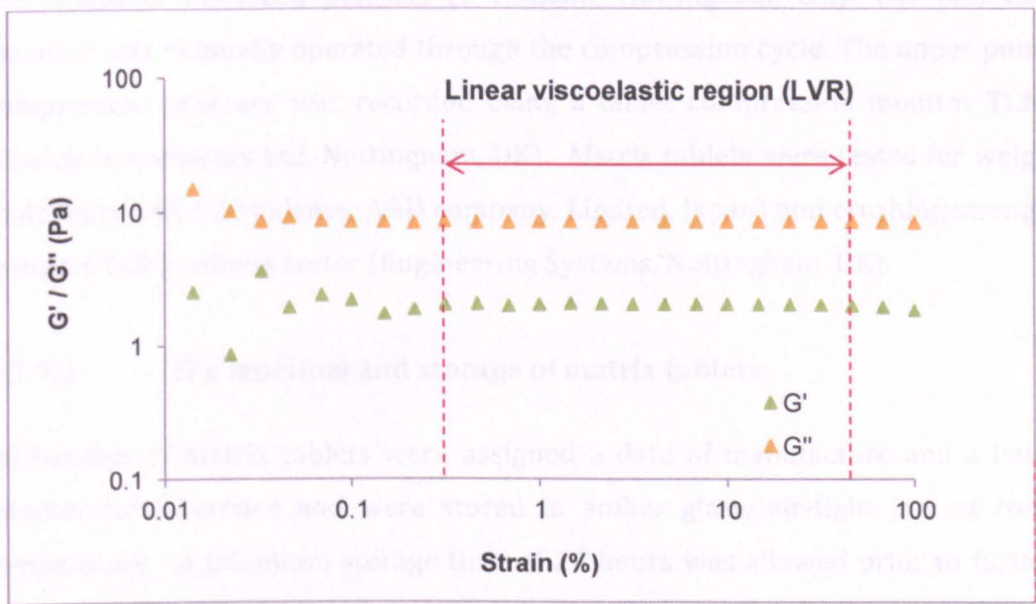


Figure 2.6 Dynamic amplitude sweep on a 2%w/w HPMC solution with respect to storage modulus (G') and loss modulus (G''). The linear viscoelastic region (LVR) is identified. Frequency 0.5Hz. Temperature 20 \pm 0.1 $^{\circ}$ C. This test was conducted for all polymer solutions.

2.2.7 The manufacture of HPMC hydrophilic matrix tablets

2.2.7.1 The preparation of formulation blends

Formulation compositions are provided in the relevant experimental chapters. Powder blends for each formulation (batch size 50 or 100 tablets) were prepared by mixing the required amounts of each ingredient in a 50 (or 100mL) glass container using a Turbula2TF mixer (Glen Creston Ltd, Middlesex, UK) for 15 minutes. After mixing, the blends were stored in airtight container prior to tableting.

2.2.7.2 The manufacture of matrix tablets

Matrix tablets weighing 250 ± 5 mg were manufactured using a Manesty F3 single punch tablet press (Manesty, Liverpool, UK) at standardised compression pressure (160 MPa for the organic salts study and 280MPa for the surfactant study), using 8 mm diameter flat-faced punches (I. Holland, Nottingham, UK). The tableting machine was manually operated through the compression cycle. The upper punch compression pressure was recorded using a tablet compression monitor TCM1 (Copley Instruments Ltd, Nottingham, UK). Matrix tablets were tested for weight uniformity (HR-120 balance, A&D company, Limited, Japan) and crushing strength using a CT40 hardness tester (Engineering Systems, Nottingham, UK).

2.2.7.3 The labelling and storage of matrix tablets

All batches of matrix tablets were assigned a date of manufacture and a batch number for reference and were stored in amber glass, air-tight jars at room temperature. A minimum storage time of 24 hours was allowed prior to further testing, to allow any post-compression relaxation to occur.

2.2.8 Dissolution testing of matrix tablets

Drug release from HPMC matrices was determined in USP dissolution apparatus I (basket) (Dissolutest, Prolabo, France) at 100rpm, in 900ml of helium-sparged dissolution medium at $37 \pm 0.5^\circ\text{C}$. Sampling was undertaken by a closed-loop automated dissolution system (Hewlett Packard, Waldbronn, Germany) driven by a peristaltic pump (Bennett Scientific Ltd, Weston-super-Mare, Somerset, UK). This circulated dissolution samples through 10mm flow-through quartz cells and returned them to the dissolution vessel. Drug quantification was undertaken by UV spectrometry (Agilent 8453 spectrophotometer, Agilent Technologies, Stockport, UK) at 273nm, the λ_{max} for caffeine, and with reference to a standard curve. The time taken to achieve 80% cumulative drug release ($T_{80\%}$) was estimated from the dissolution profiles by linear interpolation between the two nearest time points. The principal dissolution media used in the experiments was distilled water, but sodium chloride (NaCl), potassium chloride (KCl) solutions, and simulated gastric fluid USP without enzymes (SGF) were also used in Chapter 3. Sucrose solutions were used as dissolution media in Chapter 5.

2.2.8.1 Mathematical models for determining the drug release mechanism of HPMC matrices

In the presence of a gel layer, drug release from a HPMC matrix will occur through diffusion, erosion or a combination of these processes (Colombo et al 2000). This release mechanism has been described mathematically using a variety of models as reviewed in Chapter 1 Section 1.4.3. The power law (Korsmeyer et al 1983; Equation 2.4) is perhaps the most widely used model for gel-forming matrices. The coupled diffusion/relaxation equation (Peppas & Sahlin 1989; Equation 2.5) which distinguishes the Fickian diffusion and relaxation contributions to the mechanism, and the modified power law (Ford et al 1987; Equation 2.6) which accounts for the lag time (l) are interesting and will be investigated.

$$\frac{M_t}{M_\infty} = kt^n \quad \text{Equation 2.4}$$

$$\frac{M_t}{M_\infty} = k_1t^m + k_2t^{2m} \quad \text{Equation 2.5}$$

$$\frac{M_t}{M_\infty} = k(t-l)^n \quad \text{Equation 2.6}$$

In these equations, M_t is the amount of drug released at time t , M_∞ is the amount of drug released at infinite time, k_1 and k_2 are kinetic constants, t is the release time and n and m are diffusional exponents which have been used to describe the release mechanism. In the case of Equation 2.5, the first term of the right side describes the Fickian contribution, and the second term of the right side being the Case II relaxation.

Drug release data from the model HPMC matrix used in this thesis was fitted to Equation 2.4, 2.5 and 2.6, and the calculated parameters are shown in Table 2.1.

From this table it can be seen that the coupled diffusion/relaxation equation from Peppas and Sahlin (1989) showed that, (i) up to 40% release, relaxation and swelling dominated the drug release mechanism ($k_1 < k_2$) (ii) at about 60% drug release, diffusion and relaxation were contributing equally to the release mechanism ($k_1 \cong k_2$) (iii) whereas at about 80-95% drug release, the release mechanism was mainly Fickian diffusion ($k_1 > k_2$).

The power law (Korsmeyer et al 1983) and modified power law (Ford et al 1987) also described the same trend: the higher the % drug release, the more dominant was Fickian diffusion (shown in the decrease of the diffusional exponent, n).

However, the purpose of comparing dissolution profiles in this thesis is to compare the relative effects of different organic salts on matrix drug release. A simpler (and more easily understandable) parameter was therefore used: the time

taken to achieve 80% cumulative drug release ($T_{80\%}$). At 80% all of the above mathematical models suggest the matrices have adopted a diffusion dominated release mechanism. Caffeine is a water soluble drug and the release mechanism is expected to be mainly by diffusion. The modified power law is the best model for describing Fickian release mechanism where $n \leq 0.5$ with an acceptable correlation coefficient ($r^2 \geq 0.997$) at 40-95% drug release. This equation was therefore selected to use as the mathematical model for describing drug release throughout this thesis.

Fitted data range*	Power law (Korsmeyer et al 1983)		Coupled diffusion/relaxation (Peppas and Sahlin 1989)			Modified power law (Ford et al 1987)	
	n	r^2	m	k_1	k_2	n	r^2
Up to 40 % release	0.707	0.9942	0.43	0.003	0.012	0.504	0.9997
Up to 60 %	0.686	0.9957	0.43	0.011	0.01	0.498	0.9992
Up to 80 %	0.654	0.9913	0.43	0.024	0.007	0.484	0.9982
Up to 95 %	0.607	0.9871	0.43	0.035	0.005	0.469	0.9976

Table 2.1: The results of fitting drug release data to some mathematical models.

* the initial datum point (15 minutes) was excluded for the modified power law.

2.2.9 Confocal laser scanning microscopy (CLSM)

Confocal laser scanning microscopy (CLSM) imaging has been developed within our group to investigate the development of the early gel layer of HPMC matrices, and to explore for example, the influence of ionic salts and sugar media on gel layer formation (Bajwa et al 2006; Pygall et al 2008; Williams et al 2009). In the current study, this technique was used to investigate the effect of surfactants on gel morphology and the processes involved in early gel layer formation.

2.2.9.1 Theory of CLSM

The CLSM is a fluorescence microscope in which the image is obtained by laser scanning, and confocal optics which prevent out-of-focus light contributions from the specimen and markedly improve image sharpness. The CLSM has a point laser light source which raster-scans the specimen and constructs a point-by-point image based on the fluorescent response of the sample. The advantages of this technique are high sensitivity and selectivity, good spatial resolution and the potential for non-invasive optical sectioning and 3-dimensional reconstructions (Sheppard & Shotton 1997; Holmes & Cheng 2006).

The principal components and functioning of a confocal microscope is illustrated by Figure 2.7. A laser beam at the excitation wavelength passes through a high numerical illuminating aperture and then is reflected by a dichroic mirror to the objective lens. The laser beam is then focused, by the objective lens, at a specific point within a narrow focal plane within the specimen. The fluorescence emitted from the laser-specimen interaction is collected by the objective and filtered by the beam splitter. The emitted fluorescence wavelengths are directed through a pinhole aperture to the photo multiplier tube (PMT) in the detector. A narrow confocal aperture permits only fluorescent light in the focal plane to enter the detector, and therefore out-of-focus light from above and below the focal plane contributes very little to the final image. This increases the resolution of the acquired image. The final image is transferred from the PMT to a computer and the fluorescent intensities in the image are coded using colours or a greyscale.

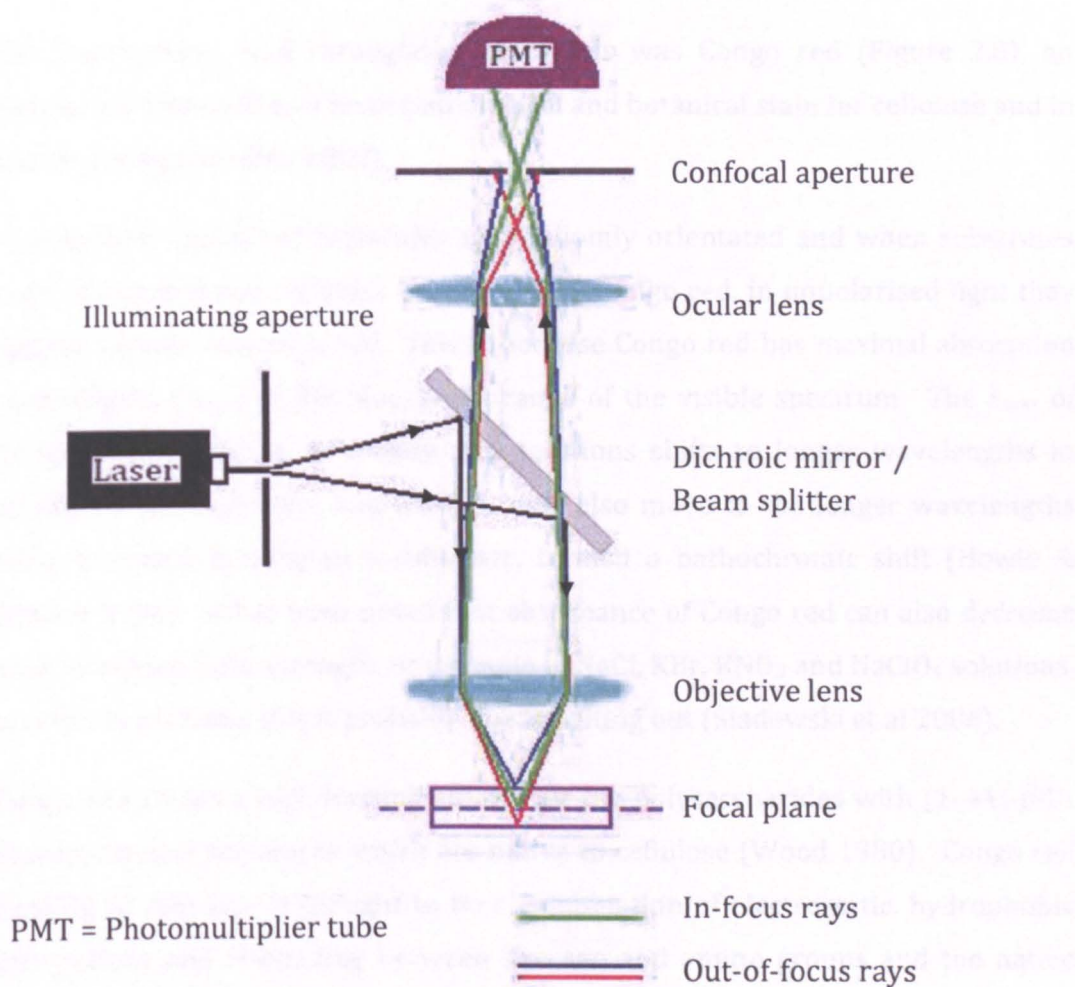


Figure 2.7 Schematic diagram of the principal elements and light paths within a confocal laser scanning microscope. Adapted from Sheppard and Shotton (1997).

2.2.9.2 Congo red

The fluorophore used throughout this thesis was Congo red (Figure 2.8), an anionic azo dye used as a histo-pathological and botanical stain for cellulose and in textile dyeing (Horobin 2002).

In solutions, Congo red molecules are randomly orientated and when substrates such as amyloid and cellulose are stained by Congo red, in unpolarised light they appear various shades of red. This is because Congo red has maximal absorption wavelengths (λ_{\max}) in the blue/green range of the visible spectrum. The λ_{\max} of Congo red in alkaline or weakly acid solutions shifts to longer wavelengths in strongly acid conditions, and the λ_{\max} may also move to the longer wavelengths with increased binding to a substrate, termed a bathochromic shift (Howie & Brewer 2009). It has been noted that absorbance of Congo red can also decrease with increased ionic strength, for example in NaCl, KBr, KNO₃ and NaClO₄ solutions, and this is probably due to salting out (Sladewski et al 2006).

Congo red shows a high binding affinity for the polysaccharides with (1→4)- β -D-glucopyranosyl sequences which are native to cellulose (Wood 1980). Congo red binding to cellulose is thought to be a combination of electrostatic, hydrophobic interactions and H-bonding between dye azo and amino groups and the native cellulose fibres. The adsorption of Congo red on cellulose has been described as follows: Firstly, a monolayer of Congo red molecules is formed on the surface of native cellulose sequences, in which the initial rate of adsorption depends upon the availability of active sites. When the monolayer reaches saturation, there is a further increase due to multilayer adsorption (Yamaki et al 2005).

Cellulose is a linear poly(glucose) in which there is a regular spacing of identical atoms along the chain. This is probably an important factor for the sorption of Congo red molecules. In the case of HPMC, the degree substitution varies along the chain to the extent that it is thought to contain significant regions of unsubstituted native cellulose, and this is probably why HPMC also responds to Congo Red staining. Binding also causes the dye to fluoresce, making Congo Red a useful fluorophore. In addition, both cellulose and HPMC swell on hydration, the polymer

is significantly expanded and more binding sites become accessible. As a result, Congo red can be used to highlight regions of hydrated HPMC when whilst fluorescence remains low in the surrounding solution (Mirza et al 1996; Pygall et al 2007).

This effect has been exploited by Bajwa et al (2006) who used confocal microscopy with Congo red to selectively identify hydrating regions within a developing gel layer. He found that 0.008% w/v Congo red in the hydration medium provided excellent resolution of individual particles within the emerging gel without significant effects on polymer swelling and hydration.

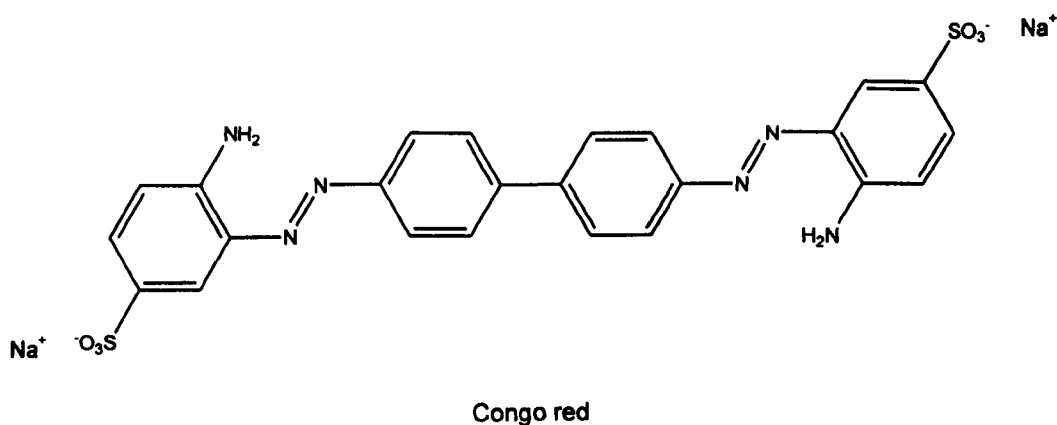


Figure 2.8 The chemical structure of Congo red.

2.2.9.3 Operational method

Confocal laser scanning microscopy (CLSM) was carried out using a Bio-Rad MRC-600 confocal microscope (Hemel Hempstead, UK) equipped with a 15mW Krypton Argon laser, a Nikon Optiphot upright microscope and a 4x/0.13NA air objective. Early gel layer formation was observed up to 15 minutes, using the method developed by Bajwa et al (2006). Figure 2.9 shows the sample geometry. Matrices were positioned in a "Fixed Observational Geometry" (FOG) sample cell between two Perspex® discs and secured by three acrylic screws. The lower surface of the upper disc was coated with a water repellent (Sigmacote®) to prevent ingress of hydration medium between the tablet and the Perspex disc surface. The FOG apparatus was positioned within a temperature-controlled hydration vessel ($37\pm1^{\circ}\text{C}$) to allow the gel layer formation to be observed from above for the first 15 minutes of tablet hydration. Measurements of radial swelling were quantified with respect to time using the method of Bajwa et al (2006) and Image Pro Plus v6.2 (Media Cybernetics, USA) software. A grid of ten evenly spaced horizontal lines was superimposed over the image, and measurements of length at each time interval, were made between the outer edge of the gel layer and the original dry matrix boundary at $t=0$ minutes. This provided the mean thickness of the apparent gel layer with respect to time. Imaging experiments were performed in triplicate, using three separate tablets.

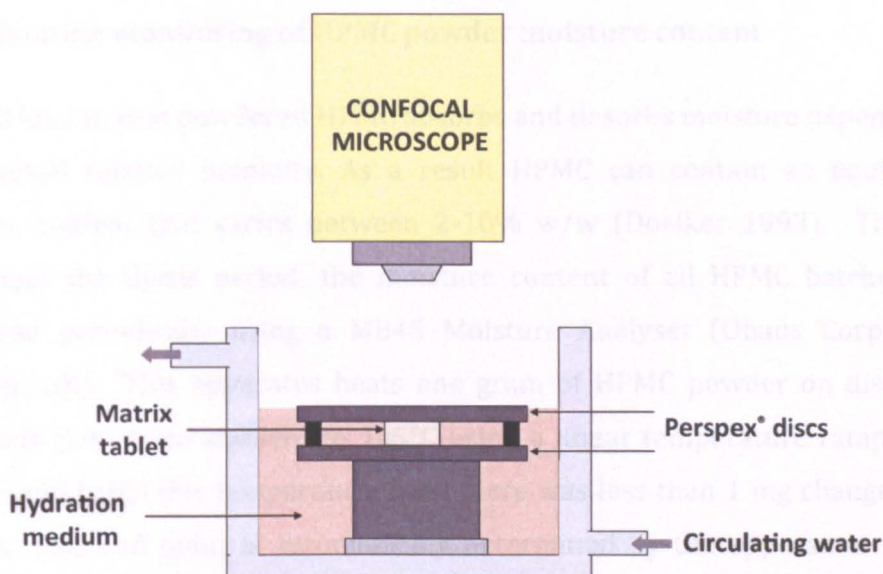


Figure 2.9 Schematic diagram of the experimental geometry used during confocal imaging, "Fixed Observational Geometry" (FOG).

Matrices are hydrated in a hydration medium containing the fluorophore, maintained at 37°C. This geometry permits the observation of gel layer development from above while the matrix undergoes radial hydration. Adapted from Bajwa et al (2006).

2.2.10 Routine monitoring of HPMC powder moisture content

It is well known that powdered HPMC absorbs and desorbs moisture depending on the external relative humidity. As a result HPMC can contain an equilibrium moisture content that varies between 2-10% w/w (Doelker 1993). Therefore throughout the thesis period, the moisture content of all HPMC batches were monitored periodically using a MB45 Moisture Analyser (Ohaus Corporation, Leicester, UK). This apparatus heats one gram of HPMC powder on disposable aluminium pans from ambient to 105°C using a linear temperature ramp over 3 minutes and holds this temperature until there was less than 1 mg change over 2 minutes. This end point is automatically determined by the apparatus. Results (see Appendix 2) showed that the moisture content was in the range 2.6-3.7% w/w throughout the the thesis work.

Chapter 3

The Effect of Organic salts on HPMC Solutions

3.1 Rationale

Many organic species are used as drug counter-ions. Examples include maleate, propionate and tartrate and these salts are chosen above their inorganic counterparts, as they exhibit better stability, solubility, physical properties, or bioavailability. Drugs with organic counter-ions are often formulated as HPMC matrix tablets, but the influence of the counter-ion on the formulation has, to date, not been the focus of any systematic studies. It is hoped that the study of the effect of organic salts on HPMC will be useful in providing further formulation guidance for HPMC matrices.

3.2 Introduction

3.2.1 Previous studies of additives affecting the properties of HPMC solutions

The effects of additives on the properties of HPMC have been widely studied. One of the most important characteristics of HPMC is the reversible thermal gelation that occurs on heating or cooling aqueous solutions. It has been found that the sol-gel transition temperature (SGTT) of HPMC can be changed by chaotropic or kosmotropic solutes. With organic species, there is evidence that their influence depend on the relative influence of different parts of their molecular structure. For examples, small hydrophilic L-amino acids decrease SGTT, while larger and

more hydrophobic or aromatic amino acids increase SGTT (Richardson et al 2006). This was postulated to be related to the balance of ionic to hydrophobic moieties in their molecular structure. Kosmotropic solutes such as ethanol, PEG 400, and propylene glycol raised SGTT, whereas glycerol, sorbitol, and most electrolytes decreased SGTT because they possess more affinity for water and dehydrated the polymer sheath (Alderman 1984; Doelker 1987; Li et al 2005). NSAID drugs such as diclofenac Na, meclofenamate Na, and mefenamate Na were found to depress SGTT (Banks 2003; Pygall et al 2011). The internal buffering agents such as tris(hydroxymethyl) aminomethane (THAM, TRIS) and sodium citrate was found to accelerate release of the weak acid drug in both pH 1.2 and 7.5 media (Pygall et al 2009; Pygall et al 2010). Water-soluble drugs such as propranolol hydrochloride and tetracycline hydrochloride have been shown to play an active role in the swelling behaviour of HPMC and methylcellulose matrices. The mechanism for this was thought to be by 'salting in' the polymer leading to increased polymer solubility, and a more efficient diffusion barrier gel layer whereas poorly soluble drugs cannot contribute in this way (Ford et al 1993; Mitchell et al 1993a; Mitchell et al 1993d). The model of salting out and salting in behaviour or Hofmeister effect on HPMC in solutions has also been proposed for ionic solute (Mitchell et al 1990a), electrolytes (Mitchell et al 1991), amino acids (Richardson et al 2006) and inorganic salts (Alderman 1984; Bajwa 2006; Liu et al 2008). However, the effects of organic salt commonly used as counter-ions on SGTT of HPMC have not yet been reported.

3.2.2 The studies of organic acids and salts with HPMC

There are few reports of organic acids and their salts being utilised in HPMC systems. However, sodium citrates have been used as internal buffers by Pygall et al (2009) and certain organic acids, such as malic acid, fumaric acid, tartaric acid, citric acid and glutaric acid have been used as microenvironmental pH modulators for basic drugs (Kranz et al 2005; Varma et al 2005; Siepe et al 2006a; Siepe et al 2006b; Tatavatric & Hoag 2006). In each case the aim was to make pH-independent controlled release systems for drugs with pH dependent solubilities.

3.3 Chapter Aims and Objectives

In this chapter, the effect of selected organic salts which are used as drug counter-ions on HPMC solution properties are investigated with respect to (i) organic salt chain length and (ii) organic salt structure relationship. The solutions studies aimed to clarify the mechanism of interaction between these organic salts and HPMC.

In particular, the experimental work in this chapter investigates the effect of organic species on:

- The sol:gel transition temperature (SGTT)
- The viscoelastic properties
- The surface tension

of HPMC solutions.

3.4 Materials and Methods

3.4.1 Organic salts

3.4.1.1 Homologous series

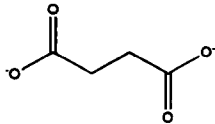
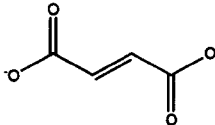
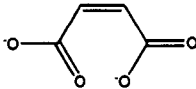
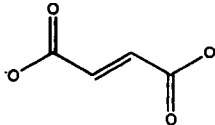
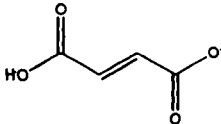

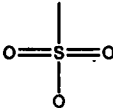
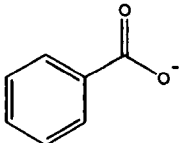
In the initial investigations, the simplest form of organic counter-ions was chosen from Table 1.3 in order to study the relationship between aliphatic chain length and their effects on HPMC. A homologous series of aliphatic organic sodium salts containing a 1-carboxylic group are shown in Table 3.1. The source and batch numbers of these materials are documented in Appendix 1.

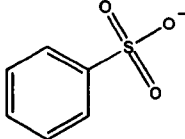
3.4.1.2 Structure activity relationships

The organic salts shown in Table 1.3 were selected and categorised according to their functional groups and structural relationships. In this chapter, the effect of these groups on HPMC were studied by comparing salts with (a) geometric isomerism (b) degree of ionisation (c) different acid functional groups (carboxylic and sulfonic acids) (d) the hydroxyl substituents and (e) the number of carboxyl groups. The selected organic salts are shown in Table 3.2. The source and batch numbers of these materials are documented in Appendix 1.

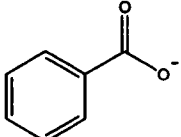
Organic salts	Chemical structure of the anion	Molecular weight (g/mol)	Solubility	pH of solution
Formate, sodium		68.01	~ 1.3 parts water	~7 (aqueous solution)
Acetate, sodium		82.03	1 g in 0.8 ml (water); 1 g in 0.6 ml (boiling water); 1 g in 19 ml (alcohol)	~7.5 - 9.2 (3% anhydrous solution)
Propionate, sodium		96.06	1 g in 1 ml (water); 1 g in 0.65 ml (boiling water); 1 g in 24 ml (alcohol)	~ 7.8 - 9.2 (2% solution)
Butyrate, sodium		110.09	soluble in water	~7-8 (aqueous solution)
Pentanoate, sodium		124.12	soluble in water	~7 (aqueous solution)
Caproate, sodium		138.14	soluble in water	~7-10 (aqueous solution)
Octanoate, sodium		166.20	freely soluble in water and acetic acid; sparingly soluble in alcohol	~8.0 - 10.5 (10% solution)

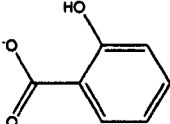
Table 3.1 The homologous series of 1-carboxyl aliphatic salts used in this chapter. All ions were used as sodium salts. (references: USP 29; Handbook of pharmaceutical excipients. 2000, Martindale 2005, Merck Index 14, Handbook of Data on Organic Compounds 1994)

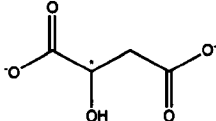
Organic salts	Chemical structure of the anion	Molecular weight (g/mol)	Solubility
(a) The effect of counter-ion geometric isomerism			
Succinate, disodium		162.05	~5 parts (water)
Fumarate disodium		160.04	soluble in water
Maleate, disodium		160.04	soluble in water
(b) The effect of counter-ion ionisation			
Fumarate, disodium		160.04	soluble in water
Fumarate, sodium hydrogen		138.06	8.5g in 100 ml (water, 25 °C)
(c) The effect of different acid functional groups : a comparison between carboxylic and sulfonic acid sodium salts			
Acetate sodium		82.03	See Table 3.1
Mesilate, sodium		118.09	soluble in water
Benzoate, sodium		144.11	1g in 1.8 ml (water), 1.4 ml (boiling water)

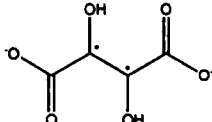
Besilate, sodium		180.16	soluble in water
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(d) The effect of hydroxyl group substituents

Benzoate, sodium		144.11	1g in 1.8 ml (water), 1.4 ml (boiling water)
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Salicylate, sodium		160.11	~ 1000 g/l (water, 20 °C)
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Malate, disodium		196.06	soluble in water
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Tartrate, disodium		230.08	~ 3 parts (cold water); 1.5 parts (boiling water)
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(e) The effect of the number of carboxylic group


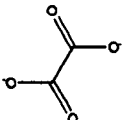
Acetate, sodium		82.03	See Table 3.1
Oxalate, disodium		134.00	27 parts (water); 16 parts (boiling water)

Table 3.2 Organic salts used in the study of structure activity relationships in this chapter. All ions were used as their sodium salts. (references: USP 29; Handbook of pharmaceutical excipients. 2000, Martindale 2005, Merck Index 14, Handbook of Data on Organic Compounds 1994)

3.4.2 HPMC

HPMC USP Type 2910 (Methocel™ E4M CR Premium EP/USP) and HPMC USP Type 2208 (Methocel™ K4M CR Premium EP/USP) were used in this study. Full details of these materials are given in Appendix 1. The quality and source of deionised water used in solution manufacture is also described in Appendix 1.

3.4.3 Manufacture of HPMC solutions

10% stock solutions were prepared by dispersing the required amount of HPMC in hot water ($> 80^{\circ}\text{C}$) using a bench-top magnetic-stirrer with hot plate (RCT basic, IKA Labortechnik Staufen, Janke&Kunkel GMBH&CO.KG, Germany). When thoroughly mixed, the dispersion was then put in an ice box to cool to room temperature while agitation was continued using a bench-top magnetic stirrer (KM02 basic, IKA® Labortechnik GMBH&CO.KG, Germany). Solutions were then stored in a refrigerator at $2-8^{\circ}\text{C}$ for at least 24 hours prior to use in order to obtain a completely hydrated solution. Previous work in our group had shown that there was little viscosity increase after 24 hours using this method.

To prepare solutions of 0.1 and 1%w/w HPMC, the required amount of 10% w/w HPMC stock solution was made up to volume by adding water. Solutions were stirred overnight and stored at $2-8^{\circ}\text{C}$ for a further 24 hours prior to use.

To prepare 0.1% and 1%w/w HPMC solutions containing different concentrations of organic salts, the following method was used. HPMC and organic salt solutions were prepared separately to avoid any interactions prior to complete dissolution or hydration. The required amount of each organic salt was completely dissolved in water about nine tenth of the final weight before incorporated into a 1%w/w HPMC stock solution about one tenth of the final weight to obtain 0.1%w/w HPMC solution (or 10%w/w HPMC stock solution to obtain 1%w/w HPMC solution). The mixed solution was then stirred until homogeneous, and stored at $2-8^{\circ}\text{C}$ for at least 24 hours prior to use.

3.4.4 Turbidimetric determinations

The sol:gel transition temperature (SGTT) of 1%w/w HPMC solutions containing organic salts were determined by turbidimetry in Cloud Point Apparatus (Medical Physics, Queen Medical Centre NHS trust, Nottingham, UK). 1 %w/w HPMC solutions containing different concentration of organic salts or organic acids were used. Each sample was measured in triplicate. Full details of the method are described in Section 2.2.3.

3.4.5 Surface tension measurements

Surface tension measurements were conducted at 20 ± 1 °C by the pendant drop method using a Profile Analysis Tensiometer (Sinterface tensiometer PAT1, Berlin, Germany). Replicate measurements were automatically determined 100 times on each sample and this was repeated on three separate samples of each solution. The relative standard deviations of the 100 measurements were smaller than 0.05%. Full details of the method are described in Section 2.2.4.

3.4.6 Density measurements

Density measurements on 0.1%w/w HPMC solutions containing organic salts were conducted by using a DMA 5000 oscillating U-tube Density Meter (Anton Paar, Graz, Austria). The density determination is based on measuring the period of oscillation of a vibrating U-shaped tube filled with sample, and using the relationship between the period of oscillation and the density. This relation holds as long as the sample is not too viscous. The density was obtained at 20°C and mean values (n=3) were used subsequently in the surface tension measurements. Full details of the method are described in Section 2.2.5.

3.4.7 Rheological determinations

The viscoelastic properties of HPMC solutions and HPMC solutions containing organic salts were determined rheologically using a MCR-301 Rheometer with Rheoplus software (Anton Paar, Graz, Austria). The parallel plate (PP) geometry (2°/50 mm) was used, with a gap of 1000µm. A freshly prepared sample was

applied carefully to the peltier temperature-controlled plate using a plastic pipette to avoid the air bubbles. When the geometry was lowered to the “trim position”, the excess sample was removed from the edges of the plate using a spatula. The gap was then lowered to 1000 μ m to start the test. A plastic cover with a solvent trap was placed and the sample edge was coated with low-viscosity silicone oil (Fisher Scientific, Leicestershire, UK) to limit sample evaporation. Sample testing was performed in triplicate. Full details of the method are described in Section 2.2.6.

3.4.7.1 Amplitude sweeps

Determining the linear viscoelastic region (LVR)

An amplitude test was undertaken to determine the dependence of G' and G'' on sample strain and to identify the “linear viscoelastic region” (LVR) of each sample. Samples were subjected to increasing strain from 0.01 to 100% using 25 points on a logarithmic scale and at a constant frequency (0.5Hz). The sample temperature was kept constant at $20 \pm 0.1^\circ\text{C}$ during each amplitude sweep. The strain at 1% which was within LVR was selected to use throughout the study.

Determining the rheological data at different temperatures

The amplitude sweep test was conducted to determine the G' , G'' and $\tan \delta$ of each sample at 20, 50 and 80°C . Samples were subjected to increasing strain from 0.01 to 100% using 25 points on a logarithmic scale and at a constant frequency (0.5Hz). The rheological data at 1% strain was brought to compare the effect of each salt on HPMC solutions.

3.4.7.2 Frequency sweeps

The frequency sweep tests were conducted from a range of 0.01 to 10 Hz using 22 points on a logarithmic scale at a constant strain (1% which is within the LVR). The sample temperature was kept constant at $20 \pm 0.1^\circ\text{C}$ during each frequency sweep. Measurements were made in triplicate.

3.4.7.3 Temperature sweeps

Temperature sweeps were performed over the range of 20 - 80°C at a heating rate of 1°C min⁻¹. Prior experiments undertaken using different rates of heating had established this as an optimum heating rate. Tests were carried out at a constant strain of (1%, within the LVR) and a constant frequency (0.5Hz). Measurements were made in triplicate.

3.4.8 Statistical analysis

Statistical differences between rheological profiles were determined using a Student's t Test (JMP 7 software, SAS Institute Inc., Cary, NC). A *p* value of less than 0.05 was considered statistically significant.

3.5 Results and Discussion

3.5.1 The effect of organic salts on the sol:gel transition temperature (SGTT) of HPMC solutions

3.5.1.1 Homologous series of salts

The sol:gel transition temperatures (SGTT) of 1%w/w HPMC solutions containing various concentrations of different aliphatic acid sodium salts were determined turbidimetrically by measurement of cloud point temperatures. Figure 3.1 shows cloud point salt concentration relationships for HPMC E4M and Figure 3.2 for HPMC K4M. The cloud point values showed a linear dependency on salt concentration (Table 3.3) but the gradients of these lines (ΔCPT) varied with the aliphatic chain length of the salt. Solutions pH was also measured and showed no correlation with CPT (no data shown). Figure 3.1(a) and 3.2(a) show that the effect on HPMC E4M and K4M showed a similar trend in which this homologous series of aliphatic acid sodium salts influenced the SGTT of HPMC solution in rank order of hydrocarbon chain length (Figure 3.1(b) and 3.2(b)). Short chain-length anions (C1-C4) were found to decrease the cloud point values, whereas the longer chain-length anions (C6-C8) increased cloud point. The crossover point was between C5 and C6 and pentanoate sodium (C5) had the least effect on HPMC solution.

For the short chain anions containing 1-4 C-atoms, these salts may alter the cloud point of HPMC by depleting polymer hydration. Their behaviour appears to correlate with the Hofmeister series observed for simple inorganic salts in which anions restructure water in the polymer hydration sheath, inducing a “salting out” effect (Touitou & Donbrow 1982b). These results support previous studies of inorganic salts which can restructure water by structure-making properties through rearrangement of the clathrate-like water structures surrounding methoxyl rich regions of the HPMC polymer chain (Bajwa et al 2006).

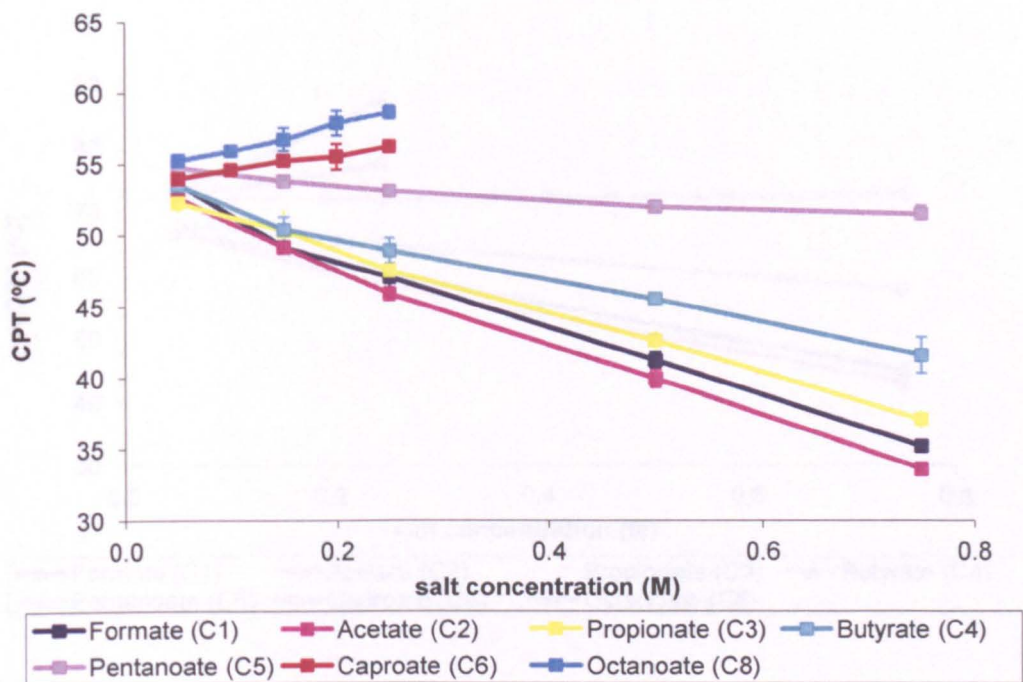
In the case of aliphatic salts containing 6-8 C-atoms, these salts appear to enhance HPMC hydration, possibly through interaction with hydrophobic regions. This

suggests behaviour analogous to previous solution studies of amino acids (Richardson et al 2006). These studies indicated that the ability of the charged ion to destabilise the polymer hydration sheath is opposed, with increasing chain length, by the ability of the hydrophobic chain to interact with and methoxyl-rich regions and polymer hydration is thereby improved by a process analogous to solubilisation.

Aliphatic salts	HPMC E4M solution		HPMC K4M solution	
	ΔCPT ($^{\circ}\text{C}/\text{M}$)	r	ΔCPT ($^{\circ}\text{C}/\text{M}$)	r
Formate sodium	-25.90	0.995	-34.17	0.995
Acetate sodium	-27.70	0.996	-36.43	0.992
Propionate sodium	-22.76	0.996	-27.29	0.999
Butyrate sodium	-17.05	0.988	-16.85	0.982
Pentanoate sodium	-4.75	0.972	1.48	0.912
Caproate sodium	5.95	0.945	24.30	0.999
Octanoate sodium	15.59	0.988	65.99	0.994

Table 3.3 Organic salts: The linear correlation (r) and slope (ΔCPT) of curve between aliphatic salts concentration and cloud point temperature (CPT). These values were obtained from Figures 3.1 and 3.2. r is the correlation coefficient.

(a)



(b)

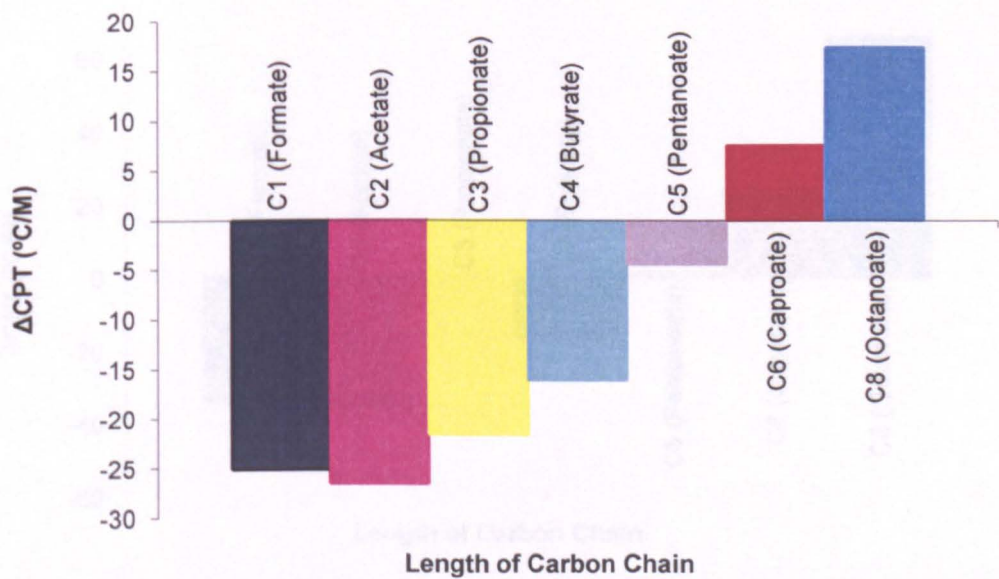


Figure 3.1 Effect of the homologous series of salts on SGT of HPMC E4M. The effect of (a) concentration (b) chain length of dissolved organic sodium salts on the sol:gel transition temperature (SGTT) of 1%w/w HPMC E4M solution. SGT expressed as cloud point temperature (CPT, °C). Temperature ramp rate of 1.5°C/min. Mean (n=3). ΔCPT obtained from the gradient of curve in figure 3.1(a).

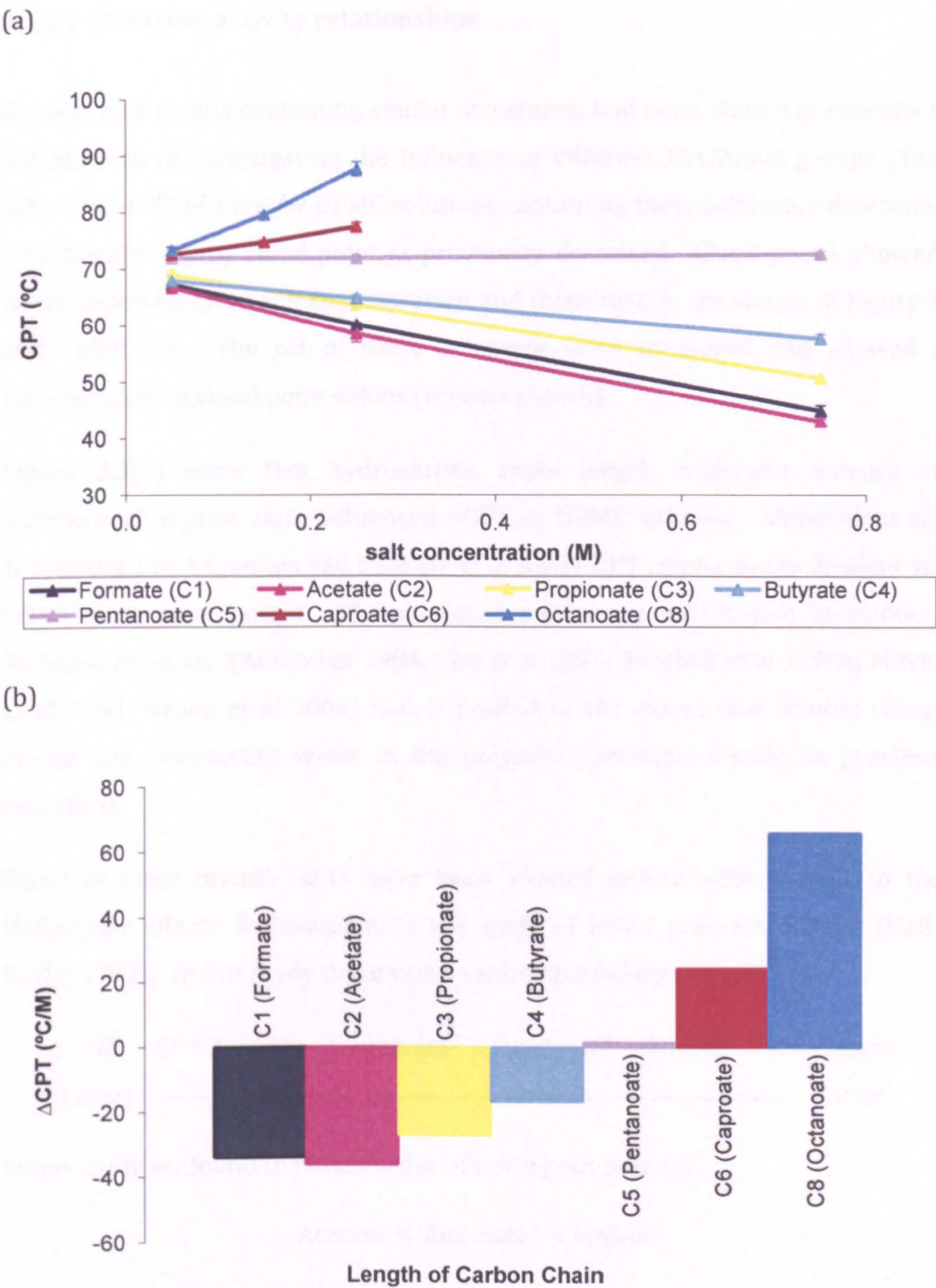


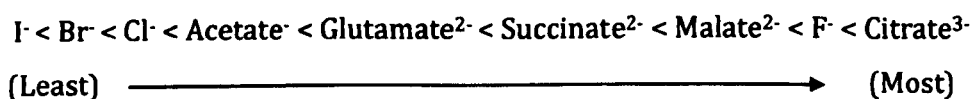
Figure 3.2 Effect of the homologous series of salts on SGTT of HPMC K4M. The effect of (a) molar concentration (b) chain length of dissolved organic sodium salts on the sol:gel transition temperature (SGTT) of 1%w/w HPMC K4M solution. SGTT expressed as cloud point temperature (CPT, °C). Temperature ramp rate of 1.5°C/min. Mean (n=3). Δ CPT obtained from the gradient of curve in figure 3.2(a).

3.5.1.2 Structure activity relationships

Organic acid anions containing similar structures, had been chosen previously for the purpose of investigating the influence of different functional groups (Table 3.2). The SGT_T of 1%w/w HPMC solutions containing these salts were determined turbidimetrically by cloud point as previously described. Cloud points showed a linear dependency on salt concentration and these results are shown in Figure 3.3 and Table 3.4. The pH of these solutions were measured and showed no correlation with cloud point values (no data shown).

Figure 3.3(b) show that hydrocarbon chain length, molecular valency and structure of organic salts influenced SGT_T of HPMC solution. Monovalent salts containing 1 to 4 C-atoms had little effect to lower CPT comparing to divalent salts which were more potent. These valency effects are well-known in studies of 'Hofmeister Series' (Alderman 1984; Cho et al 2006; Mitchell et al 1990a; Mitchell et al 1991; Bajwa et al 2006) and is related to the extent that soluble charged anions can restructure water in the polymer hydration sheath, as previously described.

Some of these organic salts have been studied before with respect to their Hofmeister effects, for example, in the study of HSV-I protease activity (Hall & Darke 1995). In this study there was a rank order salting out effect of:



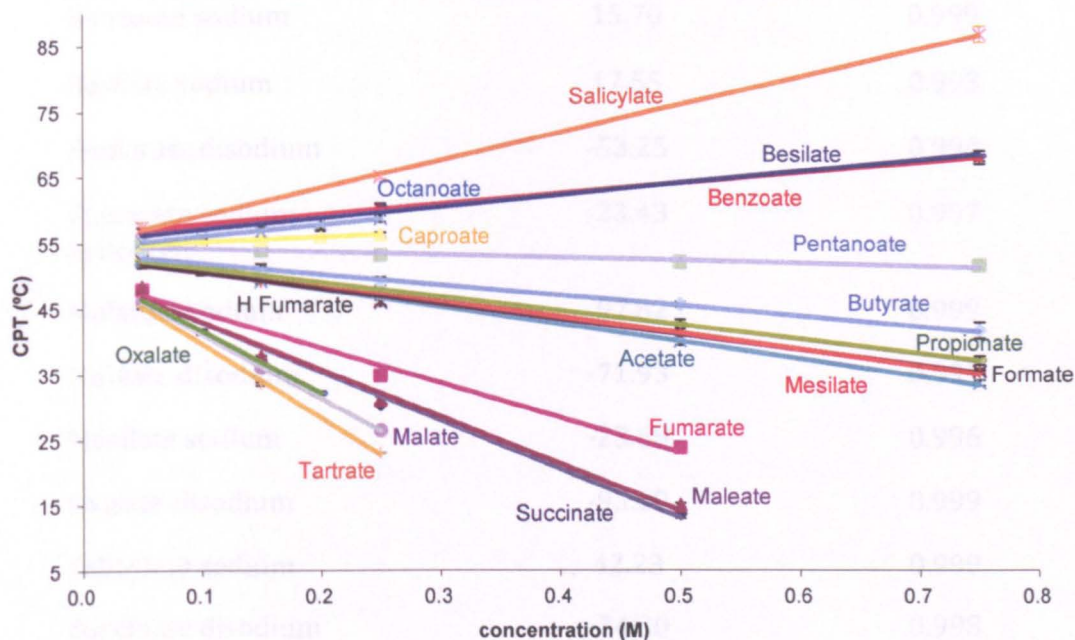
In our study we found the same order of salting out potency:



Both succinate and malate contain 4 C-atoms, but malate also contains a hydroxyl group (-OH) and was more potent than succinate. This potency-structure relationship will be discussed in next section.

Aromatic organic salts, including benzoate, besilate and salicylate, were exceptional cases. These salts elevated CPT possibly by enhancing HPMC hydration by acting as hydrotropes. Hydrotropes are compounds that can change a turbid macromolecular dispersion into a transparent solution and hydrotropic action is attributed to a 'salting in' effect (Matero 2002). These aromatic organic salts could self-associate in water to form the stacking rings with π - π interactions (Balasubramanian et al 1989; Sindkhedkar et al 2000; Waters 2002; Sasaki et al 2006; Desai & Parikh 2009; Hao et al 2012) which can enhance the solubility of organic compounds such as polymer if present at a sufficient amount.

(a)



(b)

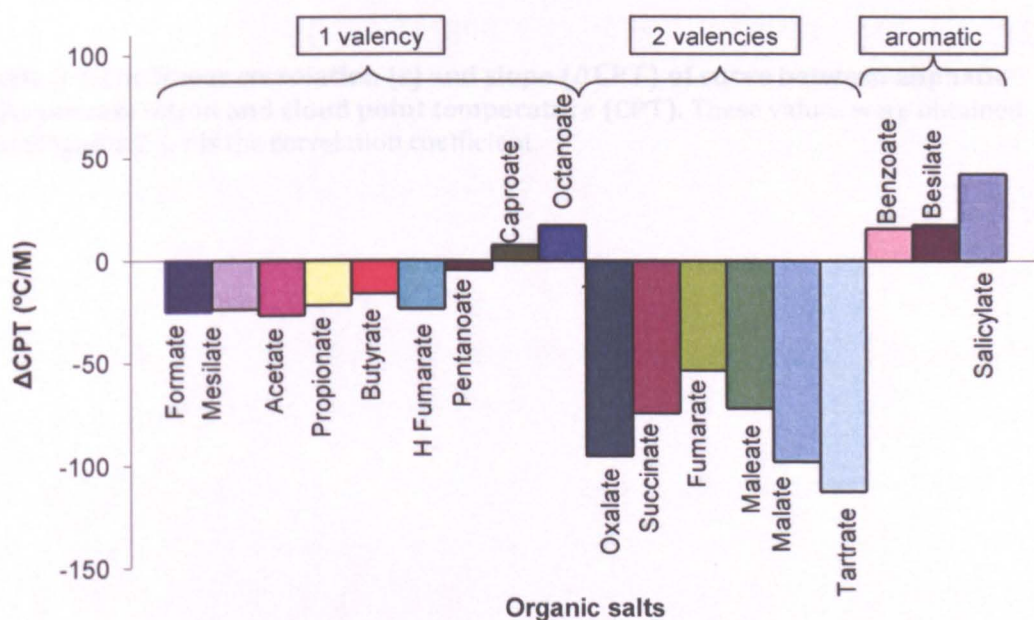


Figure 3.3 Effect of the organic salts on SGTT of HPMC E4M. The effect of (a) concentration (b) chain length of dissolved organic sodium salts on the sol:gel transition temperature (SGTT) of 1%w/w HPMC E4M solution. SGTT expressed as cloud point temperature (CPT, °C). Temperature ramp rate of 1.5°C/min. Mean (n=3). ΔCPT obtained from the gradient of curve in figure 3.4(a).

Organic salts	ΔCPT ($^{\circ}\text{C}/\text{M}$)	r
Benzoate sodium	15.70	0.999
Besilate sodium	17.55	0.993
Fumarate disodium	-53.25	0.994
Fumarate sodium hydrogen	-23.43	0.997
Malate disodium	-97.82	0.999
Maleate disodium	-71.93	0.993
Mesilate sodium	-23.68	0.996
Oxalate disodium	-95.09	0.999
Salicylate sodium	42.23	0.999
Succinate disodium	-74.30	0.998
Tartrate disodium	-112.22	0.999

Table 3.4 The linear correlation (r) and slope (ΔCPT) of curve between aliphatic salts concentration and cloud point temperature (CPT). These values were obtained from Figures 3.3. r is the correlation coefficient.

3.5.1.3 The effect of functional groups and anion structure

Several comparisons can be made of the effects of different structures and functional groups on SGTT. Although we only have a few members of each group, we can compare the effects of (a) geometric isomerism, (b) a comparison between carboxylic and sulfonic groups, (c) the hydroxyl group substituents and (d) number of carboxyl groups in the weak acid anion. From the results in Figure 3.3 we can devise some simple rules.

Rule 1: Divalent salts are more potent than monovalent salts.

Figure 3.4 compares different effect of monovalent and divalent salts on SGTT of HPMC solutions. Divalent salts (oxalate diNa, succinate diNa and fumarate diNa) exhibited a greater ability than monovalent salts (acetate Na, butyrate Na and fumarate NaH) to depress SGTT of HPMC solutions. This suggests they had a greater ability to potentiate phase separation because the divalent salts are more highly charged, and further up the Hofmeister series. This corresponds to the study of inorganic salts, phosphate and citrate buffers (Mitchell et al 1991; Kujawinski 2000; Liu et al 2008; Pygall et al 2009).

Rule 2: Valencies, substitutions and geometric isomerism influence the ability of organic salts on altering HPMC thermogelation.

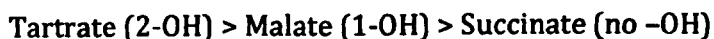
Figure 3.5 compares the ability of 4 C-atom organic salts which possess different valencies, substitutions and geometric isomerism to alter SGTT of HPMC solutions. These differences lead to the different physical properties of organic salts, and hence their ability to restructure polymer hydration sheath which may exert Hofmeister's series. The species with more affinity to water have more potential to dehydrate HPMC and thus depress its SGTT.

Rule 3: Carboxylic and sulfonic groups show little difference in their effects.

Figure 3.6 compares the effect of salts containing carboxylic and sulfonic groups. There was no different effect between acetate (carboxylic) and mesilate (sulfonic) or benzoate (carboxylic) and besilate (sulfonic). The strong similarity may be due to the monovalent character of both acid groups, however the sulfonic acid group ($pK_a = 1.9$) is a stronger acid than carboxylic acid ($pK_a = \sim 3.9$) and may therefore exert monovalent ion-effects on SGTT in the solutions of lower pH.

Rule 4: Adding more hydroxyl groups, increases potency of the ion.

Figure 3.7 show how the different hydroxyl groups substituents (-OH) influence the effect on SGTT of HPMC solutions. Salicylate (1-OH) was more potent than benzoate (no -OH) in elevating the SGTT of HPMC solution. In contrast, the potency of kosmotropic ions in depressing the SGTT of HPMC solution were rank ordered as follows:



These rank orders may simply have arisen as a result of the small number of anions investigated. However, increasing numbers of hydroxyl groups, provide more potential for interaction with the hydrogen bonded structure of water, and so it is not surprising that additional -OH groups enhance the effects of the parent molecule. However, studies of soluble hydroxyl-rich species such as sugars (Williams et al 2009) show that the orientation of the hydroxyl group is also an important factor. Sugars in which the -OH group disrupts water structure have an enhanced kosmotropic effect.

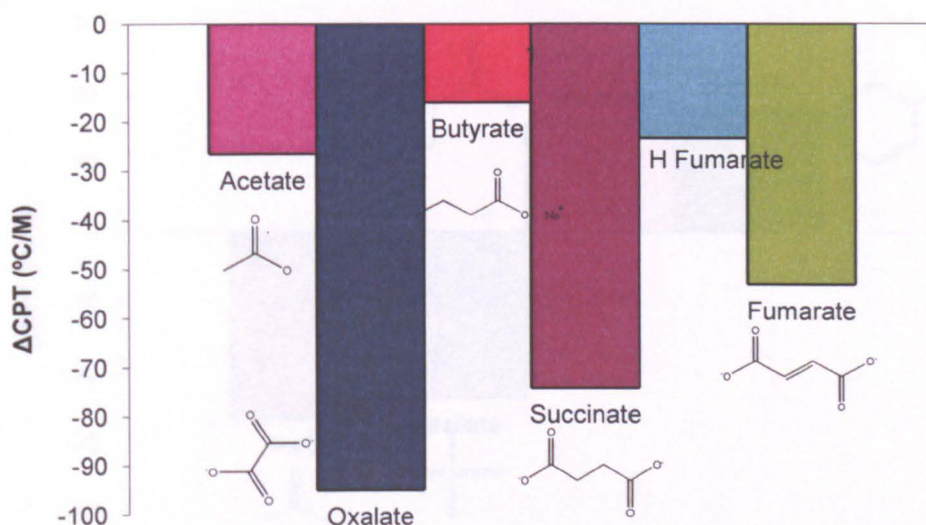


Figure 3.4 The effect of the number of carboxyl groups of the organic salts on the sol:gel transition temperature (SGTT) of 1%w/w HPMC E4M solution. SGTT expressed as cloud point temperature (CPT, °C). Temperature ramp rate of 1.5°C/min. Mean (n=3). ΔCPT obtained from the gradient of curve in figure 3.4(a).

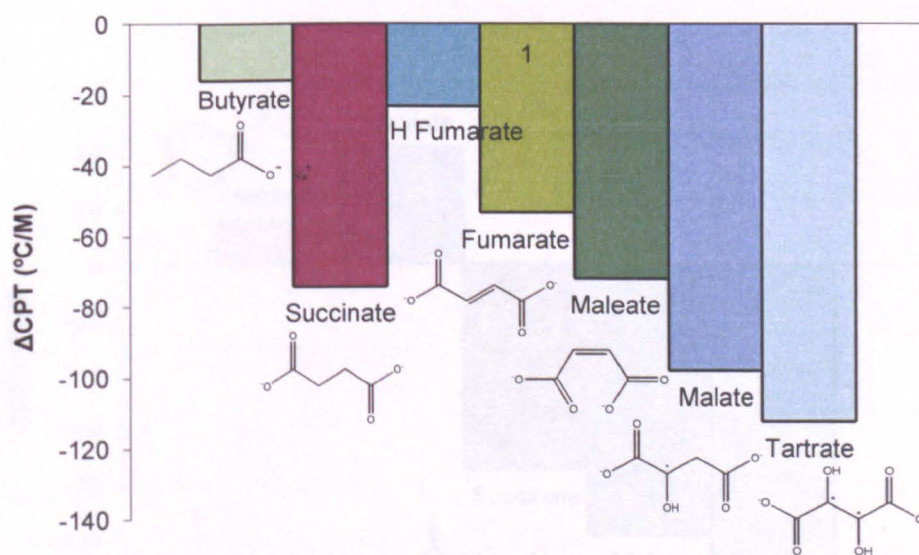


Figure 3.5 The effect of organic salts containing 4 C-atoms on the sol:gel transition temperature (SGTT) of 1%w/w HPMC E4M solution. SGTT expressed as cloud point temperature (CPT, °C). Temperature ramp rate of 1.5°C/min. Mean (n=3). ΔCPT obtained from the gradient of curve in figure 3.4(a).

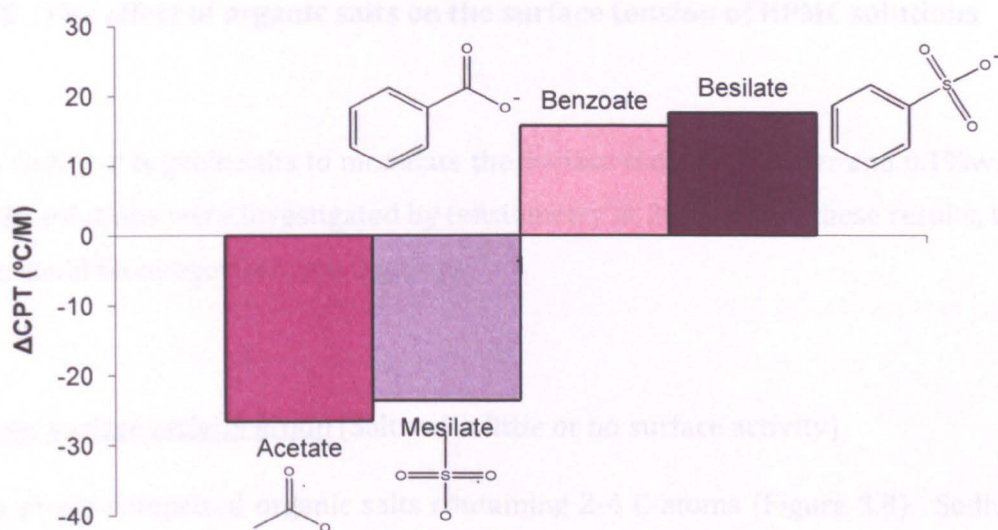


Figure 3.6 A comparison of carboxylate and sulphonate organic salts on the sol:gel transition temperature (SGTT) of 1%w/w HPMC E4M solution. SGTT expressed as cloud point temperature (CPT, °C). Temperature ramp rate of 1.5°C/min. Mean (n=3). ΔCPT obtained from the gradient of curve in figure 3.4(a).

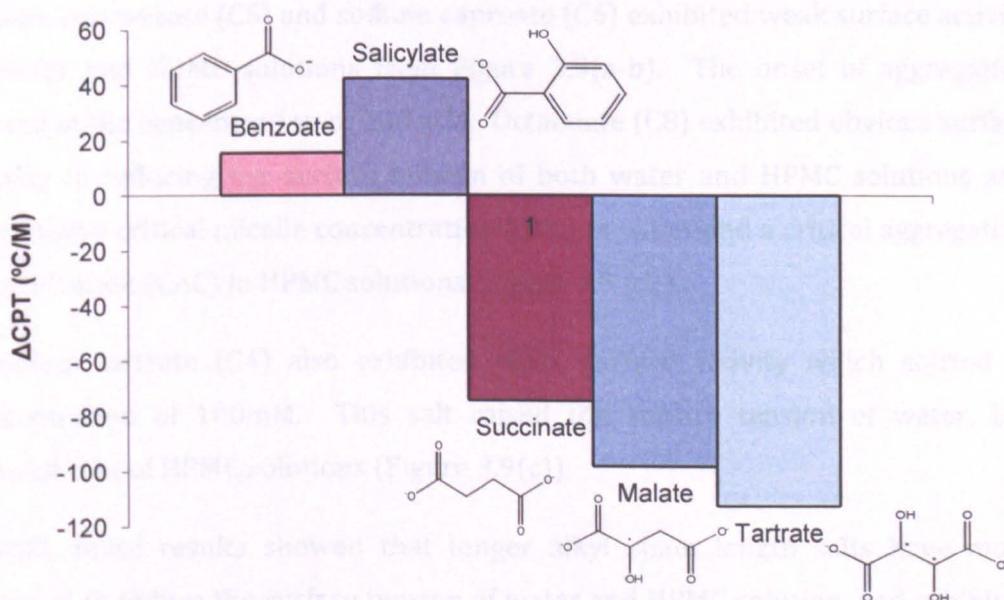


Figure 3.7 The effect of hydroxyl group substituents on organic salt molecules on the sol:gel transition temperature (SGTT) of 1%w/w HPMC E4M solution. SGTT expressed as cloud point temperature (CPT, °C). Temperature ramp rate of 1.5°C/min. Mean (n=3). ΔCPT obtained from the gradient of curve in figure 3.4(a).

3.5.2 The effect of organic salts on the surface tension of HPMC solutions

The ability of organic salts to modulate the surface tension of water and 0.1%w/w HPMC solutions were investigated by tensiometry at 20°C. From these results, the salts could be categorised into 3 groups;

a) Low surface activity group (Salts with little or no surface activity)

This group comprised organic salts containing 2-4 C-atoms (Figure 3.8). Sodium acetate (C2), sodium propionate (C3) and sodium butyrate (C4), showed no surface activity both in water and HPMC solution within the range 0-750mM, and only slightly reduced the surface tension at ~1000mM.

b) Surface-active group (Salts with clear surface activity in the range investigated)

Sodium pentanoate (C5) and sodium caproate (C6) exhibited weak surface activity in water and HPMC solutions from Figure 3.9(a-b). The onset of aggregation started at the concentration of 100 mM. Octanoate (C8) exhibited obvious surface activity in reducing the surface tension of both water and HPMC solutions and exhibiting a critical micelle concentration (cmc) in water and a critical aggregation concentration (CAC) in HPMC solutions (Figure 3.9 (d)).

Disodium tartrate (C4) also exhibited weak surface activity which started at concentration of 100mM. This salt raised the surface tension of water, but reduced that of HPMC solutions (Figure 3.9(c)).

Overall, these results showed that longer alkyl chain length salts have more potential to reduce the surface tension of water and HPMC solution, and exhibited the lower cmc and CAC. This is consequence of the increasing hydrophobicity of the anion with alkyl chain length, which has been well-documented in higher chain length surfactants (Smith & Tanford 1973; Tsao et al 1991; Lim et al 2007).

c) Aromatic group

Organic salts containing an aromatic ring showed weak surface activity in water, but little surface activity in HPMC solutions (Figure 3.10). However, sodium benzoate, sodium besilate and sodium salicylate are amphiphiles which they can self-associate in water if the concentration is high enough to form a π -stacking aggregation (Balasubramanian et al 1989; Matero 2002). This type of system does not exhibit cmc (Florence & Attwood 2009).

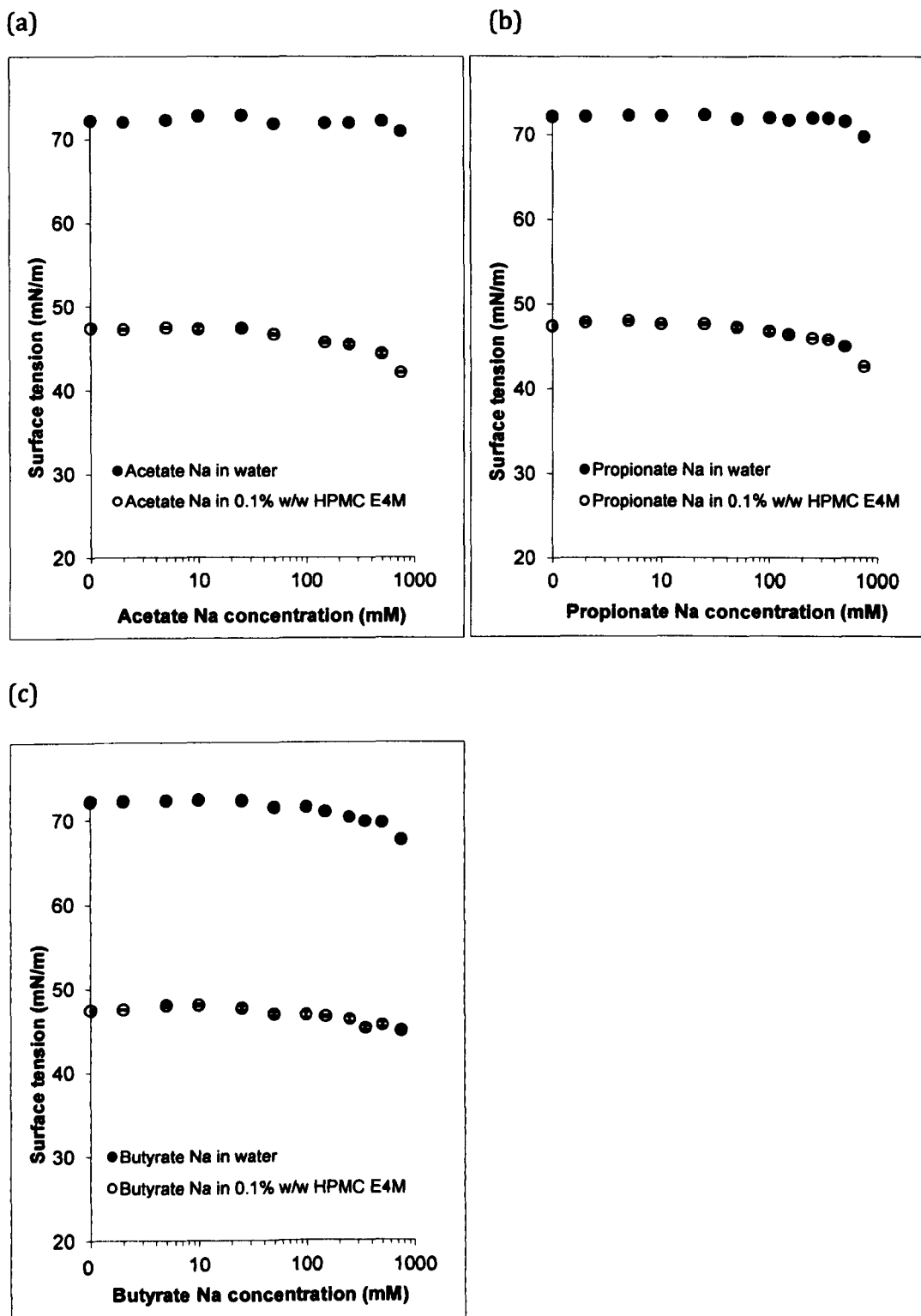


Figure 3.8 Low surface activity group - The effect of organic salt concentration on the surface tension of water and 0.1% w/w HPMC E4M solution at 20°C (a) sodium acetate (b) sodium propionate (c) sodium butyrate. Surface tension was measured by the pendant drop method. Mean ($n=3$)

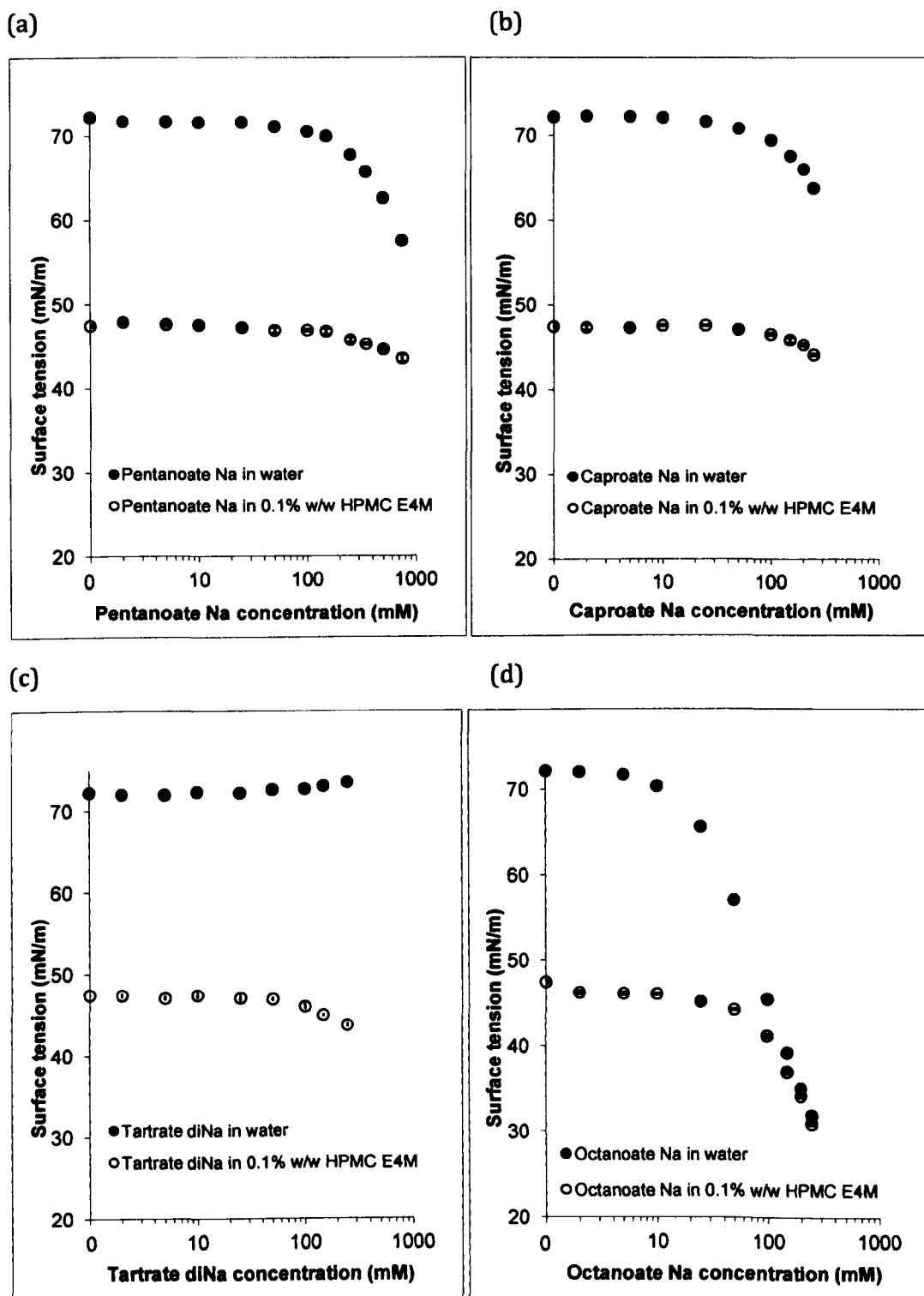


Figure 3.9 Surface active group - The effect of organic salt concentration on the surface tension of water and 0.1% w/w HPMC E4M solution at 20°C (a) sodium pentanoate (b) sodium caproate (c) disodium tartrate (d) sodium octanoate. Surface tension was measured by the pendant drop method. Mean (n=3)

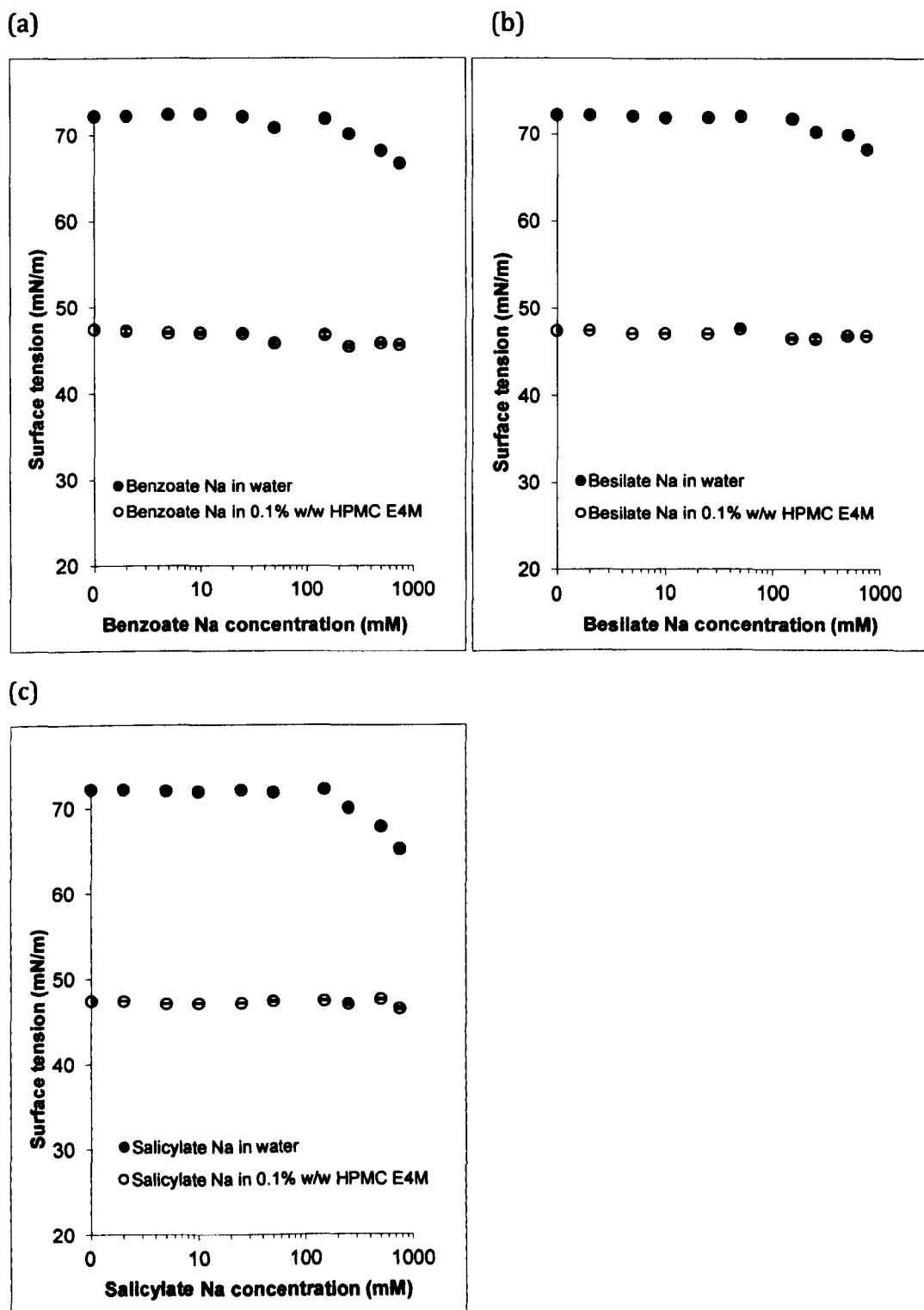


Figure 3.10 Aromatic group - The effect of organic salt concentration on the surface tension of water and 0.1% w/w HPMC E4M solution at 20°C (a) sodium benzoate (b) sodium besilate (c) sodium salicylate. Surface tension was measured by the pendant drop method. Mean ($n=3$)

3.5.3 The effect of organic salts on the viscoelastic properties of HPMC solutions

Dynamic oscillatory rheology investigates the viscoelastic properties of a solution by applying small oscillations to a sample and determining the ability of the sample to recover. This can provide the information on the internal molecular structure.

Prior to testing, the linear viscoelastic region (LVR) was determined for each sample in order to obtain the appropriate test conditions (Mezger 2006). This was determined at the same temperature as the subsequent frequency (20°C, 50°C and 80°C). The optimisation of conditions for the oscillatory rheology studies in this chapter was conducted (data not shown).

3.5.3.1 Homologous series

(a) Temperature experiment

Storage modulus (G'), loss modulus (G'') and $\tan \delta$ values for 2%w/w HPMC solutions containing acetate Na (C2), pentanoate Na (C5) and Octanoate Na (C8) were determined at different temperatures. Table 3.5 shows that at 20°C, there were only small differences between these samples, and all values were low compared with the divalent organic salts which will be discussed in the next section. At this temperature, G'' of all samples dominated which means they were liquid-like in their properties.

At 50°C, there were large differences in G' because this temperature is approaching SGTT (The SGTT of a 1%w/w HPMC solution, and HPMC solutions containing 0.5M acetate Na, 0.5M pentanoate Na and 0.25M octanoate Na are ~55, 40, 52, 59°C, respectively). At this temperature, HPMC solutions containing acetate Na and pentanoate Na showed a clear G' domination which means their characteristics are more solid-like (elastic) than liquid-like. In contrast, the HPMC solutions containing octanoate Na still exhibited G'' domination. These results correlate with their SGTT as previously mentioned.

At 80°C, all samples were G' dominated which means they were more solid in this state. The G' values were in a rank order of chain length as follows:

$$\text{Acetate (C2)} > \text{Pentanoate (C5)} > \text{Octanoate (C8)}$$

and all values were higher than HPMC solution alone. This suggests that at temperatures above the SGTT, the elastic property of HPMC solutions are enhanced by adding these salts. This effect could be due to increased competition for water of hydration, resulting in more pronounced phase separation in hydrophobic region of the gel.

(b) Frequency sweep experiment

Frequency sweep experiments were conducted at 20°C. The results are shown in Figure 3.11. Figure 3.11(a) shows the frequency dependence of the complex viscosity which can indicate the overall viscoelastic response of polymer-salt mixtures. The complex viscosity of HPMC solutions containing acetate Na and Pentanoate Na were not different from HPMC solution alone, while those of HPMC solution containing octanoate Na was manifestly lower. This suggests that HPMC solutions containing octanoate Na exhibit more liquid-like behavior. All these salts showed a weak interaction with the polymer.

Figure 3.11(b) and (c) show the frequency dependence of the storage modulus (G') and loss modulus (G'') for HPMC solutions containing acetate Na, pentanoate Na and octanoate Na. In the presence of acetate Na and pentanoate Na, there was very small increase in both G' and G'' . However, with octanoate Na, there was decrease in these mechanical moduli, suggesting that both elastic and viscous properties of these HPMC solutions were being suppressed by the octanoate Na.

The magnitude of G' is related to the gel strength of the sample. If the sample is a strongly cross-linked gel, G' would be much higher than G'' and not affected by the oscillatory frequency. In contrast, G'' would be larger than G' at some point in the frequency range if the sample is a physically entangled gel network. This is because freely entangled polymer chains can move past each other at low

frequencies so that the sample behaves like a viscous liquid, whereas there is not enough time for this network rearrangement to occur within an oscillation cycle at the higher frequencies, resulting in a predominately elastic deformation.

From these experiments, at the temperature below the SGTT, HPMC solutions containing octanoate Na appear to be behaving as a physically entangled gel with a free movement of polymer chains at 20°C. At the temperatures above the SGTT, octanoate Na appears enhance the gel structure in both elastic and viscous properties relative to HPMC alone.

Tan δ values represent the ratio of G'' to G' and provide further evidence of the changes in viscoelasticity, if $\tan \delta < 1$, indicating the potential of the sample to move towards gel-like behaviour. These salts show no apparent potential to induce gel-like behaviour in HPMC solutions (Figure 3.11 (d)).

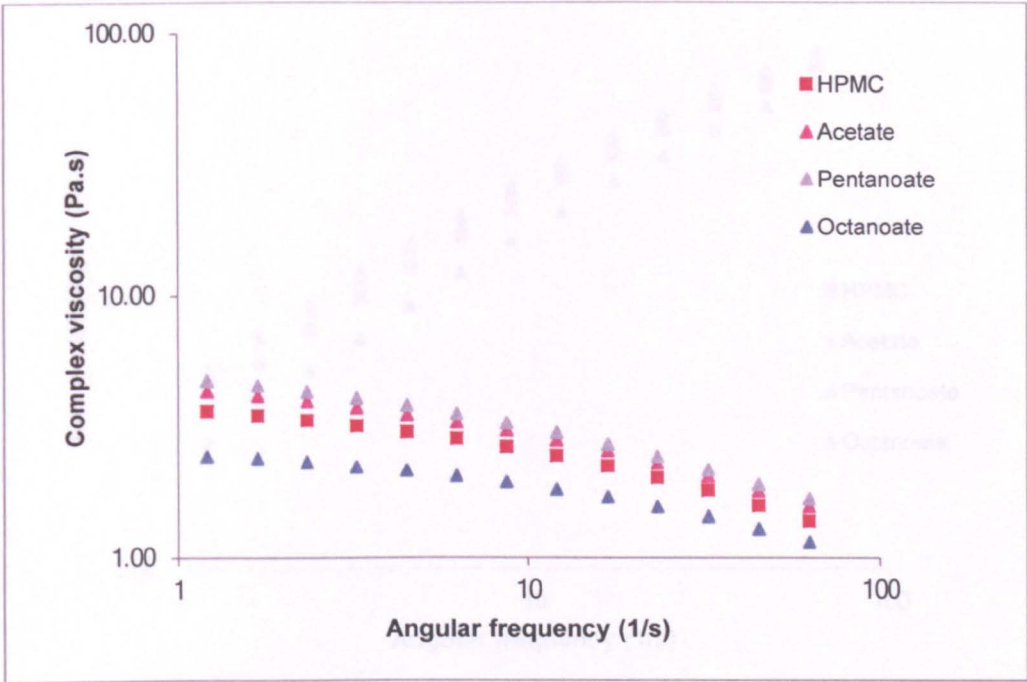
(c) Continuous range temperature sweep experiment

The temperature sweep experiment of 2%w/w HPMC solutions containing acetate Na, pentanoate Na and octanoate Na are shown in Figure 3.12. Acetate Na exhibited a very sharp crossover (gel point), with incomplete recovered on the cooling cycle. Pentanoate Na exhibited the same behavior as an HPMC solution but recovered more completely. Octanoate Na samples showed a sharp drop in G'' and G' before a rise and crossover at the gel point. It also was not fully recovered in the cooling cycle. These gel points from crossover corresponded to their SGTT determined earlier (see CPT studies in Section 3.5.1). The different slopes of these viscosity profiles suggest that HPMC solutions containing these organic salts may exhibit different mechanism of phase separation when going through the sol:gel transition.

Samples	Rheological data at different temperatures								
	20°C			50°C			80°C		
	G'	G''	tan δ	G'	G''	tan δ	G'	G''	tan δ
2% w/w HPMC	2.02	8.43	4.18	4.38	3.92	0.90	27.1	3.01	0.11
2% w/w HPMC + 0.50M Acetate Na	3.87	12.2	3.14	41.0	4.16	0.10	112	8.37	0.07
2% w/w HPMC + 0.50M Pentanoate Na	3.82	12.7	3.33	11.6	2.10	0.18	44.4	3.99	0.09
2% w/w HPMC + 0.25M Octanoate Na	2.03	9.41	4.64	0.47	3.25	6.93	34.7	10.5	0.30

Table 3.5 Rheological data of HPMC solutions (2%w/w) containing the initial homologous series of organic salts. The data obtained from amplitude sweep test at different temperatures. These are the values at 1% strain.

(a) Complex viscosity



(b) Storage modulus or elastic modulus, G'

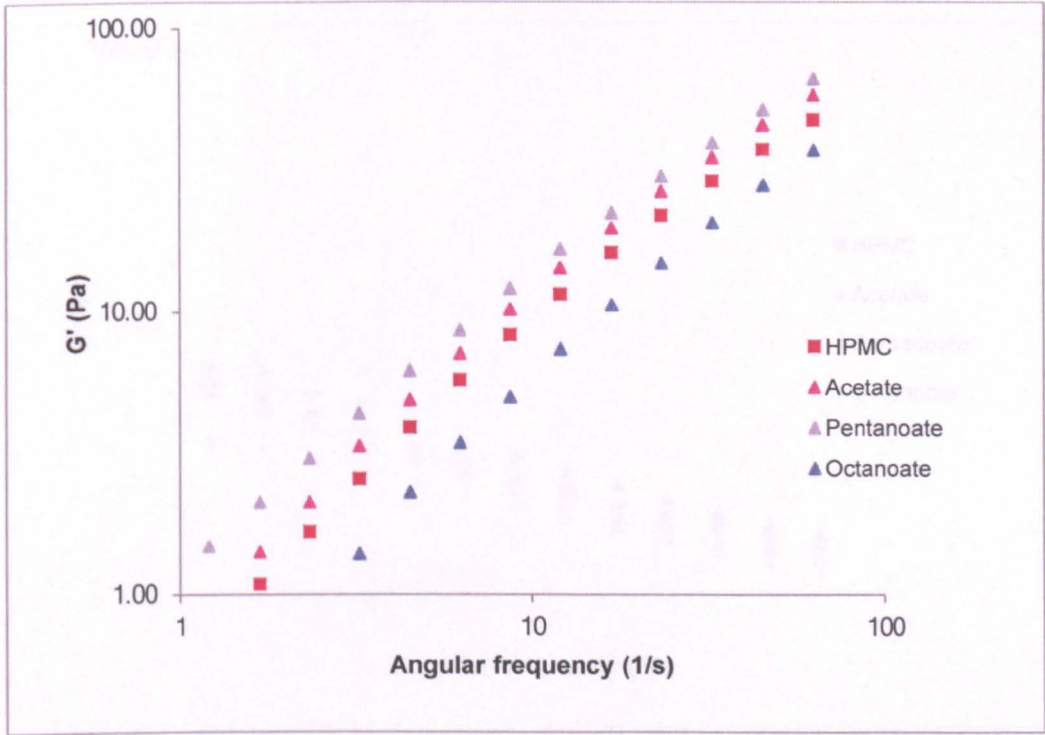
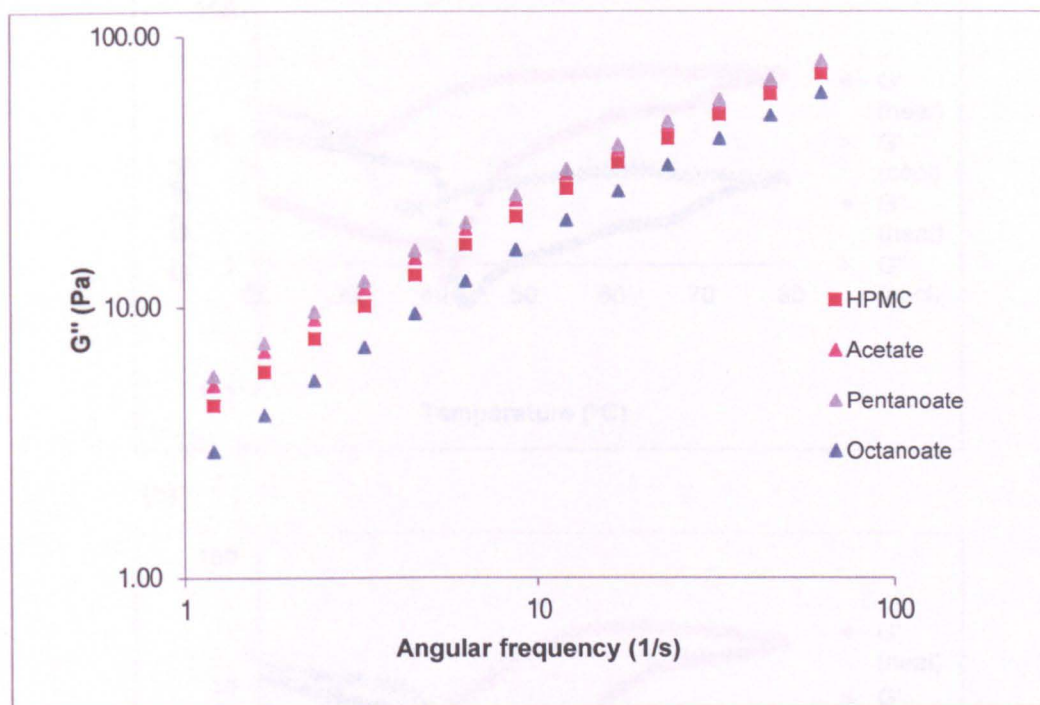


Figure 1.87 Rheological properties of (a) complex viscosity (b) elastic modulus, G' (c) storage modulus, G'' and (d) loss modulus, G'' for 1% w/w HPMC solutions containing the 10, 15, 20 and 25% w/w organic acids.

(c) Loss modulus or viscous modulus, G''



(d) $\tan \delta$

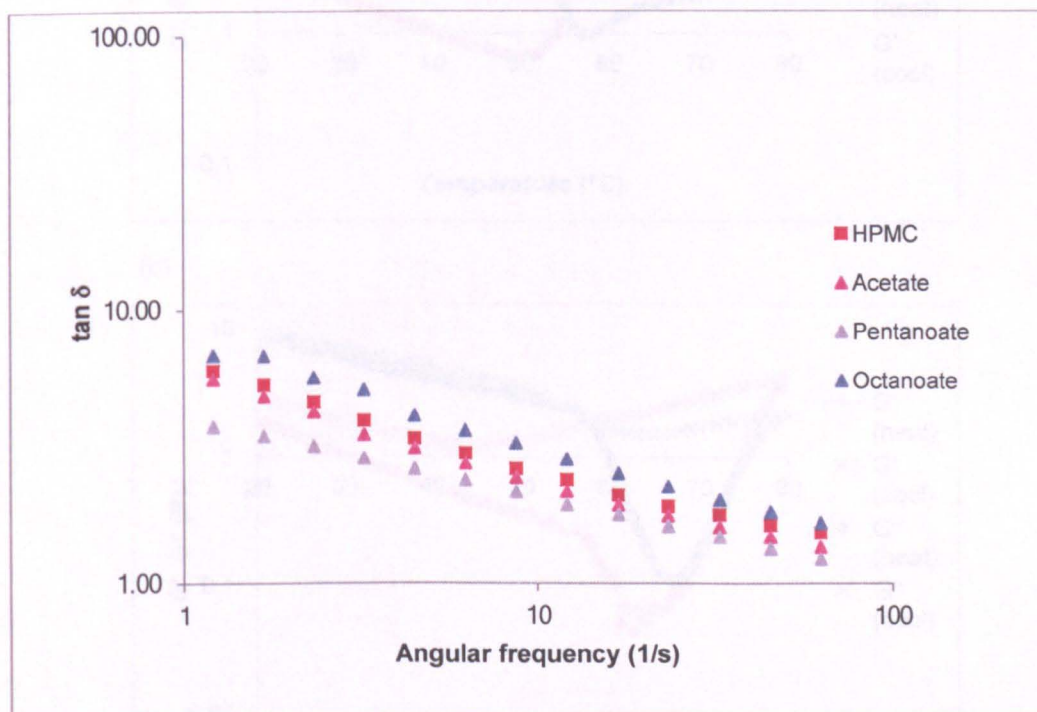


Figure 3.11 Frequency dependence of (a) complex viscosity (b) elastic modulus, G' (c) viscous modulus, G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions containing the initial homologous series of organic salts.

Geometry = PP50mm. Temperature = 20°C. Strain = 1%

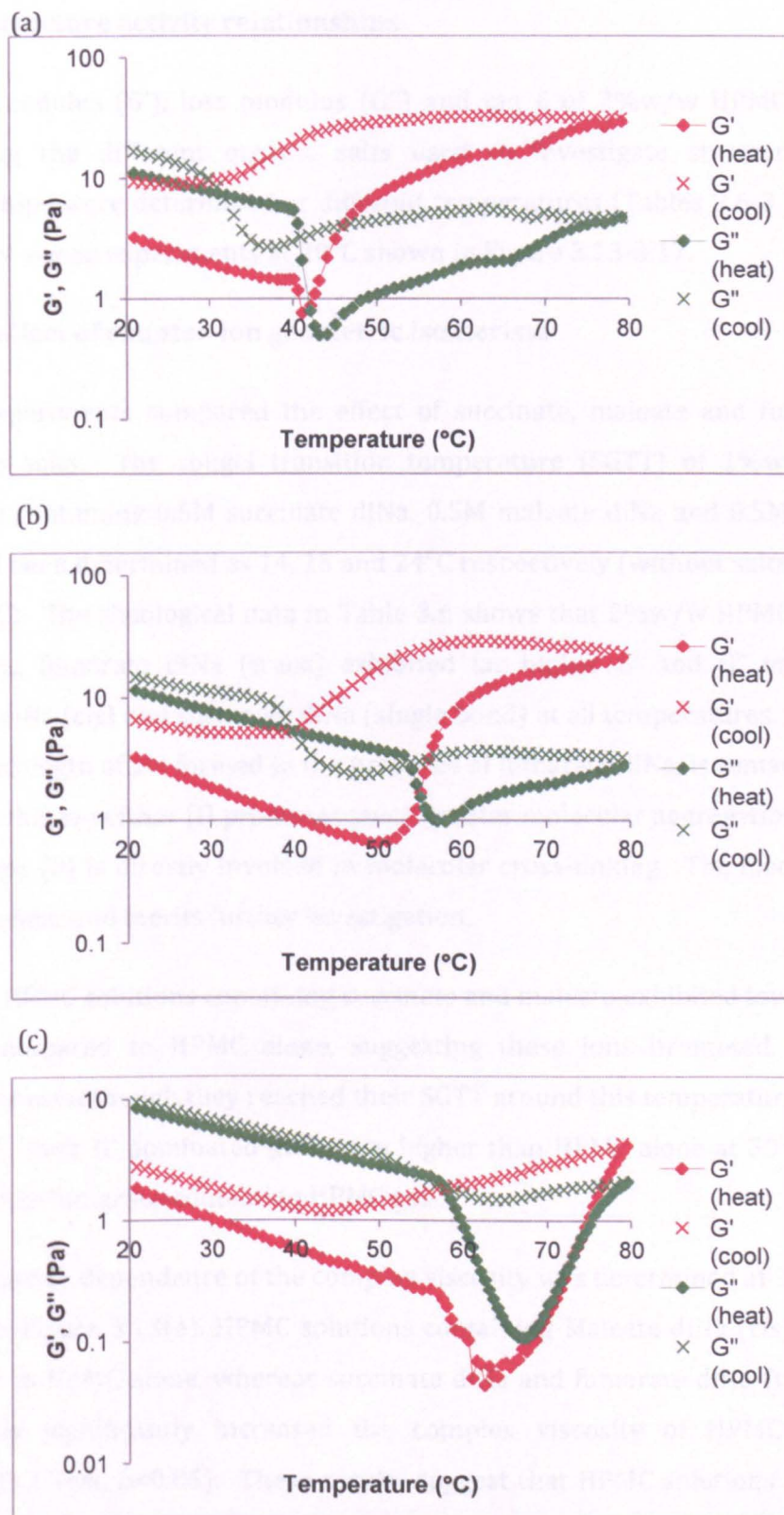


Figure 3.12 Temperature dependence of G' and G'' for 2%w/w HPMC solutions containing (a) acetate Na (b) pentanoate Na and (c) octanoate Na. Geometry = PP50mm with covered silicone oil. Heating and cooling rate = $1^{\circ}\text{C}/\text{min}$. Strain = 1%. Frequency = 0.5Hz.

3.5.3.2 Structure activity relationships

Storage modulus (G'), loss modulus (G'') and $\tan \delta$ of 2%w/w HPMC solutions containing the different organic salts used to investigate structure activity relationships were determined at different temperatures (Tables 3.6-3.10) and in frequency sweep experiments at 20°C shown in Figure 3.13-3.17.

(a) The effect of counter-ion geometric isomerism

These experiments compared the effect of succinate, maleate and fumarate as disodium salts. The sol:gel transition temperature (SGTT) of 1%w/w HPMC solutions containing 0.5M succinate diNa, 0.5M maleate diNa and 0.5M fumarate diNa had been determined as 14, 15 and 24°C respectively (without salts, the SGTT was 55°C). The rheological data in Table 3.6 shows that 2%w/w HPMC solutions containing fumarate diNa (trans) exhibited far higher G' and G'' values than maleate diNa (cis) and succinate diNa (single bond) at all temperatures. The much greater strength of gel formed in the presence of fumarate diNa, is remarkable and suggests this ion either (i) promotes much greater molecular aggregation of HPMC or perhaps (ii) is directly involved in molecular cross-linking. The mechanism of this is unclear and merits further investigation.

At 20°C, HPMC solutions containing succinate and maleate exhibited low G' and G'' values compared to HPMC alone, suggesting these ions promoted liquid-like behaviour even though they reached their SGTT around this temperature. At 50°C and 80°C, their G' dominated gels were higher than HPMC alone at 50°C, but not 80°C, unlike fumarate-containing HPMC gels.

The frequency dependence of the complex viscosity was determined at 20°C and is shown in Figure 3.13(a). HPMC solutions containing Maleate diNa (cis) were not different to HPMC alone, whereas succinate diNa and fumarate diNa (trans) salts manifestly significantly increased the complex viscosity of HPMC solutions (Student's t Test, $p < 0.05$). These results suggest that HPMC solutions containing maleate exhibit a liquid-like behaviour, indicating only a weak interaction or effect on polymer solution properties. In the other hand, those containing fumarate

(trans) and succinate predominated with solid-like (elastic) behaviour. This strong elastic response is typical for systems with well-developed association networks (Larson 2005). In this case, the trans form could have more ability than the cis form to be more involved in the network, or to condense the polymer to a denser gel, perhaps by removing water.

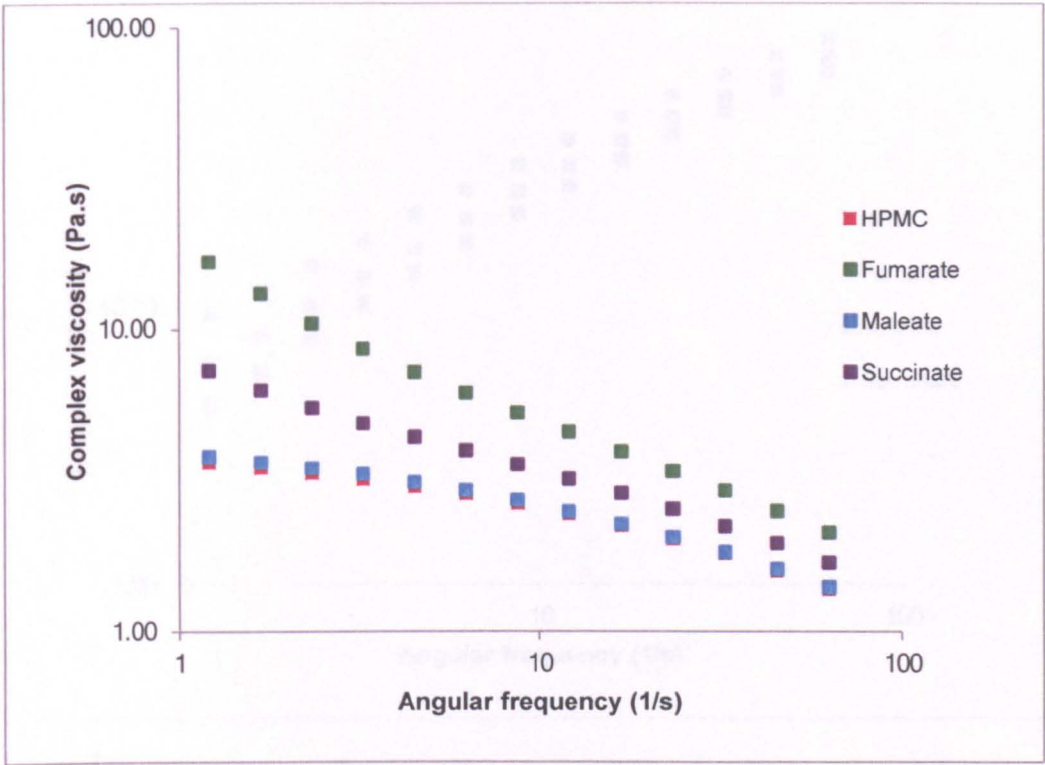
Figure 3.13(b) and (c) show the frequency dependencies of the storage modulus (G') and loss modulus (G''). The presence of maleate diNa caused no change in both G' and G'' . However fumarate diNa and succinate diNa, both increased these mechanical moduli (Student's t Test, $p < 0.05$), suggesting that both elastic and viscous properties of HPMC solution were enhanced in the presence of fumarate diNa and succinate diNa.

$\tan \delta$ values is the ratio of G'' to G' and indicates the potential of the sample to move towards gel-like behaviour ($\tan \delta < 1$). Figure 3.13 (d) exhibits the expected trend toward G' domination with increasing frequency normally seen for HPMC solutions, and this behaviour is paralleled by solutions containing maleate. Gel containing succinate and fumarate showed lower $\tan \delta$ values, a consequence of their greater G' dominance, and they were also more independent of frequency than HPMC solutions. This suggests these gels are physically different, and may have a higher degree of intermolecular linkages, perhaps a greater degree of structural development, or a greater number or stronger intermolecular bonds.

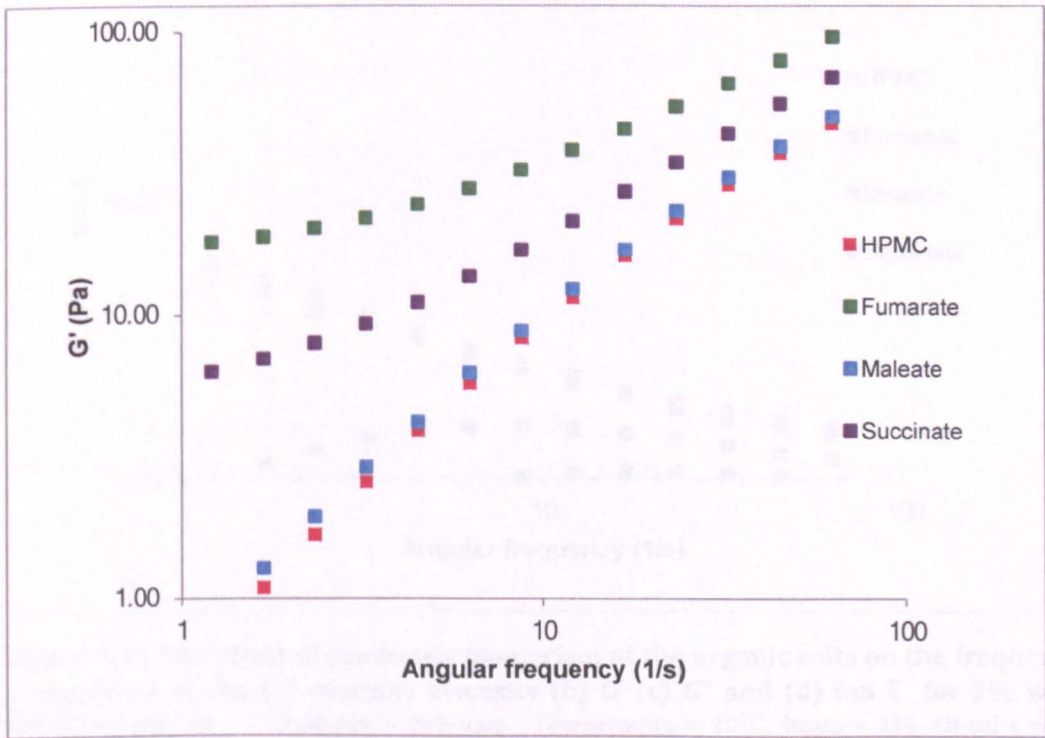
Samples	Rheological data at different temperatures								
	20°C			50°C			80°C		
	G'	G''	tanδ	G'	G''	tanδ	G'	G''	tanδ
2% w/w HPMC	2.02	8.43	4.18	4.38	3.92	0.90	27.1	3.01	0.11
2% w/w HPMC + 0.50M Succinate diNa	0.33	0.27	0.83	12.3	3.65	0.30	14.5	3.60	0.25
2% w/w HPMC + 0.50M Fumarate diNa	11.8	14.0	1.19	163	10.4	0.06	196	16.5	0.08
2% w/w HPMC + 0.50M Maleate diNa	2.64	0.85	0.32	16.9	2.74	0.16	13.8	2.24	0.16

Table 3.6 Rheological data of HPMC solutions (2%w/w) containing organic salts: the effect of geometric isomerism. The data obtained from amplitude sweeps at different temperatures. These are the value at 1% strain

(a) Complex viscosity



(b) Storage modulus, G'



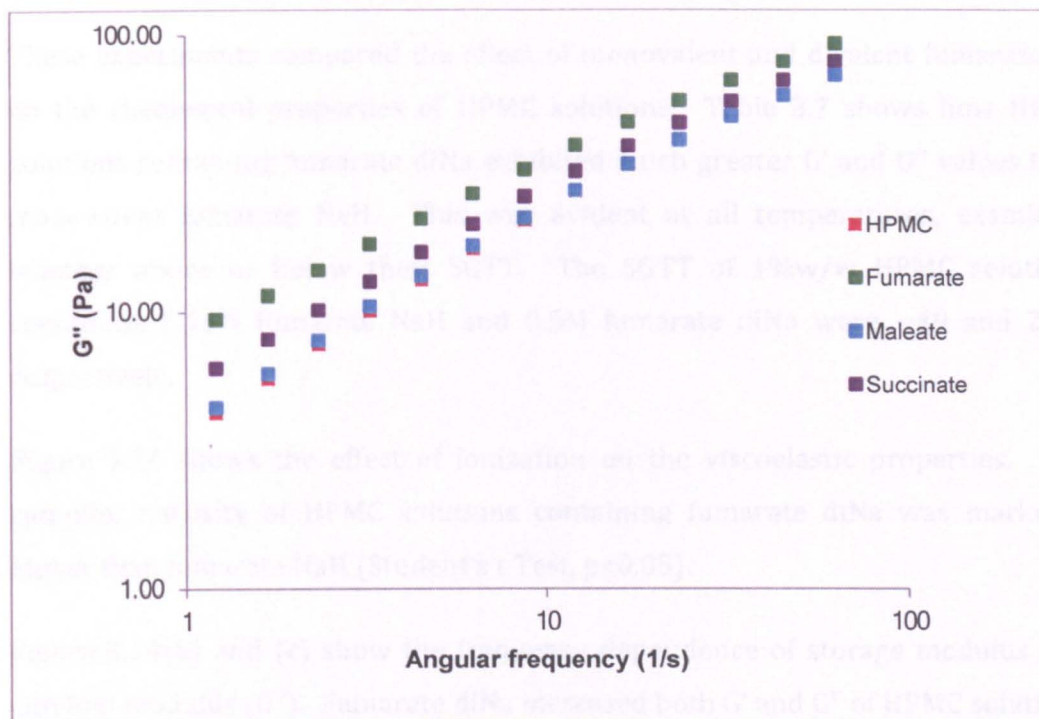
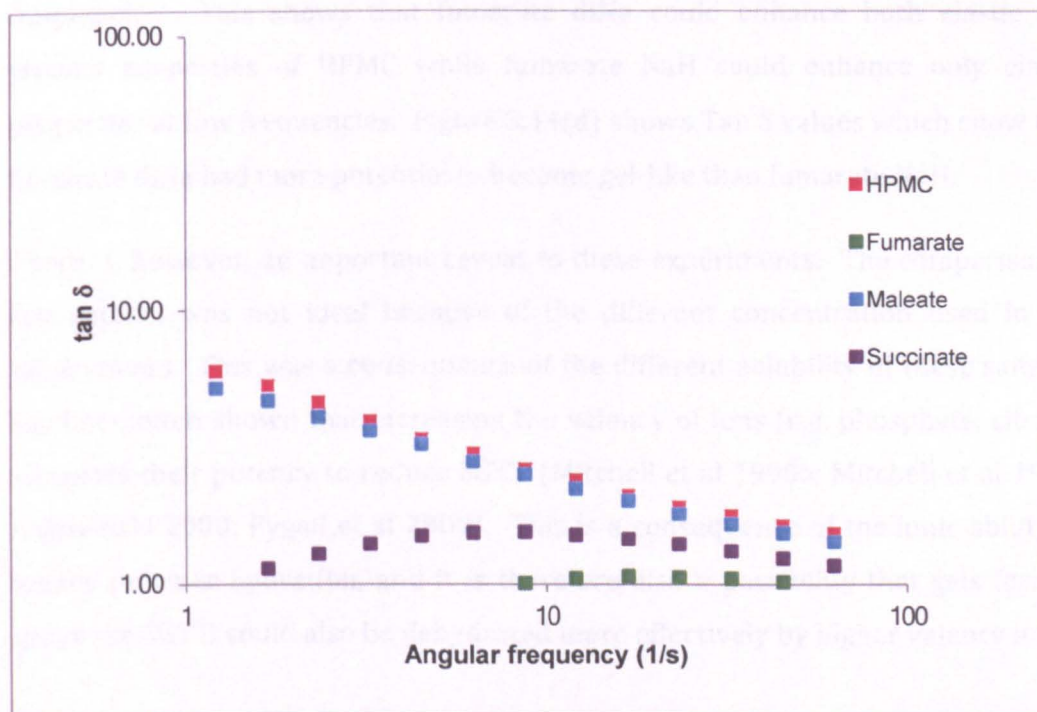
(c) Loss modulus, G'' (d) $\tan \delta$ 

Figure 3.13 The effect of geometric isomerism of the organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions. Geometry = PP50mm. Temperature = 20°C. Strain = 1%. All salts were presented at 0.5M concentration.

(b) The effect of counter-ion ionisation

These experiments compared the effect of monovalent and divalent fumarate Na on the rheological properties of HPMC solutions. Table 3.7 shows how HPMC solutions containing fumarate diNa exhibited much greater G' and G'' values than monovalent fumarate NaH. This was evident at all temperatures, examined, whether above or below their SGTT. The SGTT of 1%w/w HPMC solutions containing 0.15M fumarate NaH and 0.5M fumarate diNa were ~ 49 and 24°C respectively.

Figure 3.14 shows the effect of ionization on the viscoelastic properties. The complex viscosity of HPMC solutions containing fumarate diNa was markedly higher than fumarate NaH (Student's t Test, $p < 0.05$).

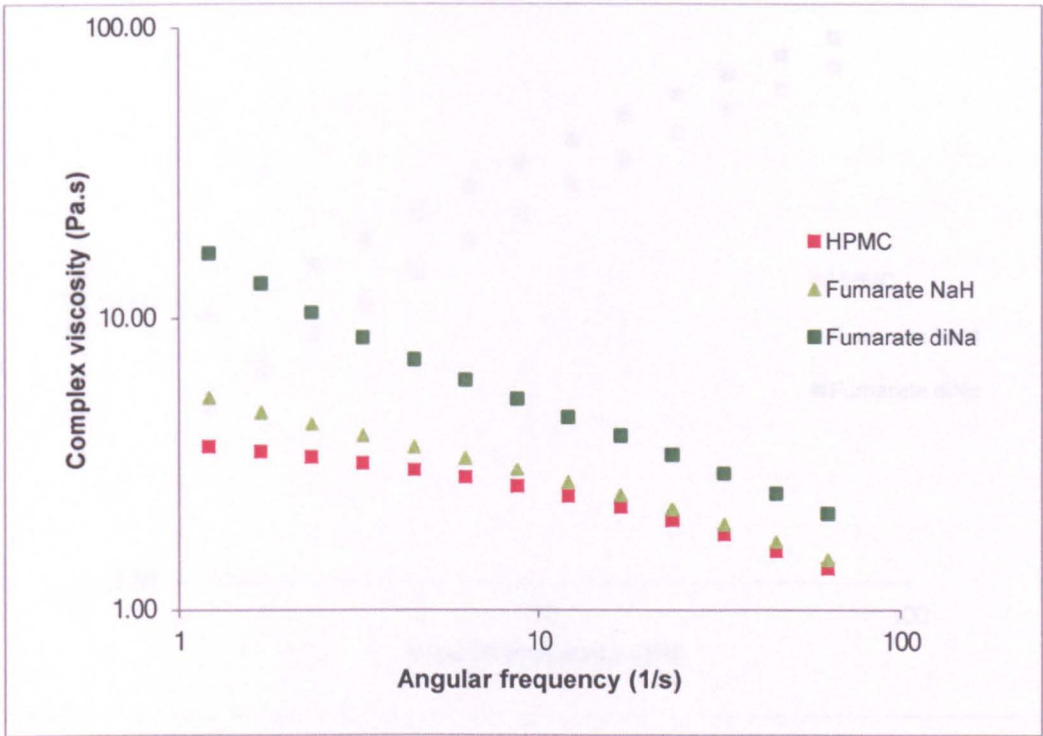
Figure 3.14(b) and (c) show the frequency dependence of storage modulus (G') and loss modulus (G''). Fumarate diNa increased both G' and G'' of HPMC solutions at all frequencies, whereas fumarate NaH increased only G' at medium to low frequencies. This shows that fumarate diNa could enhance both elastic and viscous properties of HPMC while fumarate NaH could enhance only elastic properties at low frequencies. Figure 3.14(d) shows $\tan \delta$ values which show that fumarate diNa had more potential to become gel-like than fumarate NaH.

There is, however, an important caveat to these experiments. The comparison in this section was not ideal because of the different concentration used in the experiments. This was a consequence of the different solubility of these salts. It has been often shown that increasing the valency of ions (e.g. phosphate, citrate) increases their potency to reduce SGTT (Mitchell et al 1990a; Mitchell et al 1991; Kujawinski 2000; Pygall et al 2009). This is a consequence of the ionic ability to reduce polymer hydration, and it is therefore also a possibility that gels formed above the SGTT, could also be dehydrated more effectively by higher valency ions.

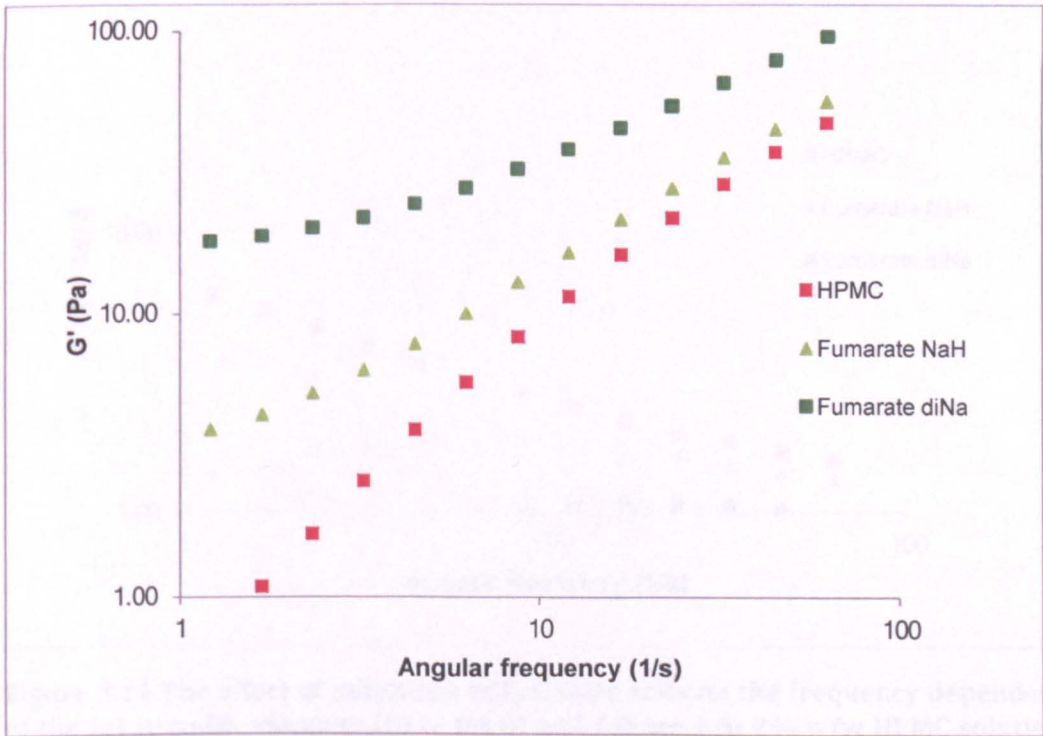
Samples	Rheological data at different temperatures								
	20°C			50°C			80°C		
	G'	G''	tanδ	G'	G''	tanδ	G'	G''	tanδ
2% w/w HPMC	2.02	8.43	4.18	4.38	3.92	0.90	27.1	3.01	0.11
2% w/w HPMC + 0.15M Fumarate Na H	2.91	10.1	3.48	11.1	4.01	0.36	30.6	3.53	0.12
2% w/w HPMC + 0.50M Fumarate diNa	11.8	14.0	1.19	163	10.4	0.06	196	16.5	0.08

Table 3.7 Rheological data of HPMC solutions (2%w/w) containing fumarate salts: the effect of ionization. The data obtained from amplitude sweeps at different temperatures. These are the value at 1% strain

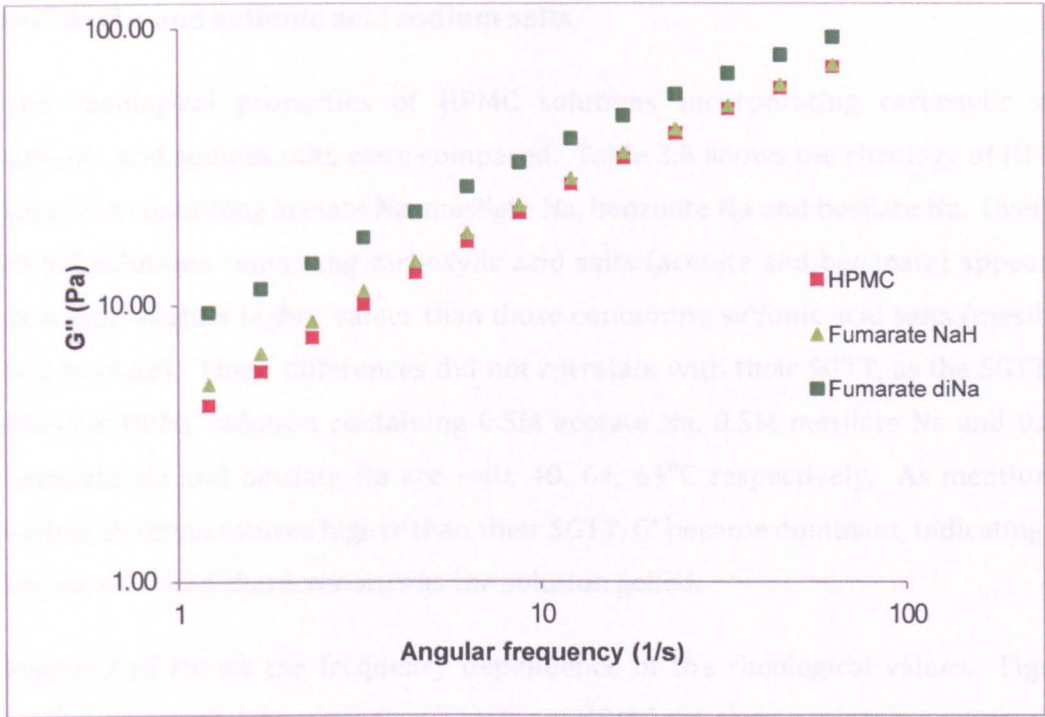
(a) Complex viscosity



(b) Storage modulus, G'



(c) Loss modulus, G''



(d) $\tan \delta$

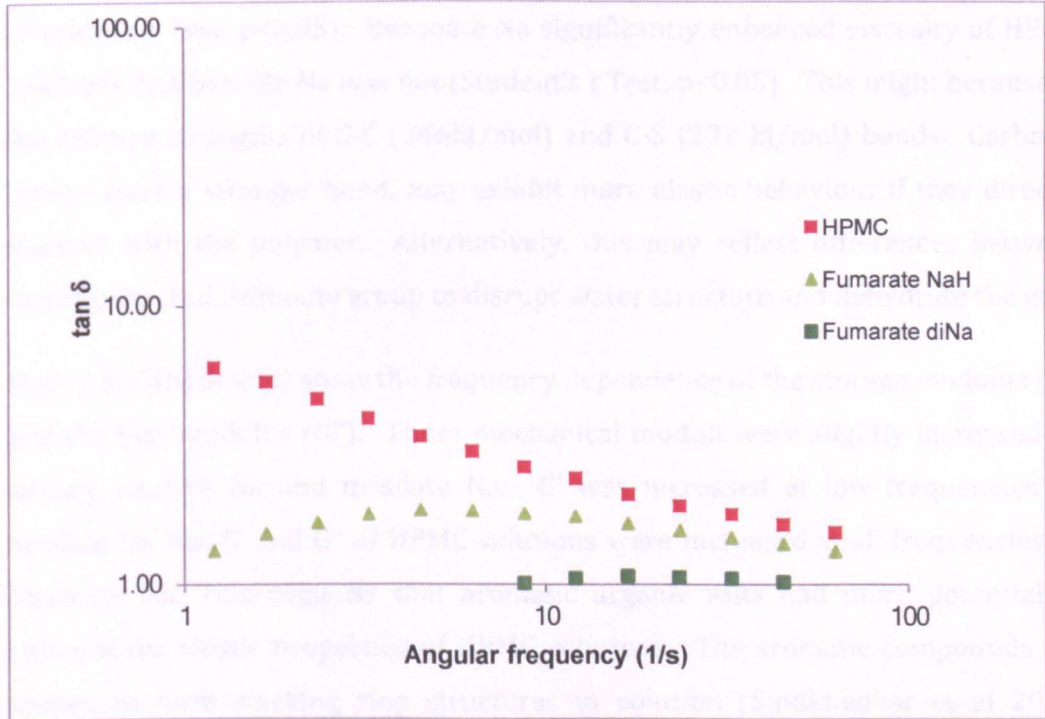


Figure 3.14 The effect of ionisation of fumarate salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ in 2% w/w HPMC solutions. Geometry = PP50mm. Temperature = 20°C. Strain = 1%. Fumarate NaH and diNa were presented at 0.15M and 0.50M concentration respectively.

(c) The effect of counter-ion functional groups : a comparison between carboxylic and sulfonic acid sodium salts

The rheological properties of HPMC solutions incorporating carboxylic and sulfonic acid sodium salts were compared. Table 3.8 shows the rheology of HPMC solutions containing acetate Na, mesilate Na, benzoate Na and besilate Na. Overall, HPMC solutions containing carboxylic acid salts (acetate and benzoate) appeared to exhibit slightly higher values than those containing sulfonic acid salts (mesilate and besilate). These differences did not correlate with their SGTT, as the SGTT of 1%w/w HPMC solution containing 0.5M acetate Na, 0.5M mesilate Na and 0.5M benzoate Na and besilate Na are ~40, 40, 64, 64°C respectively. As mentioned earlier, at temperatures higher than their SGTT, G' became dominant, indicating an increase in solid characteristics as the solution gelled.

Figure 3.15 shows the frequency dependence of the rheological values. Figure 3.15(a) shows that the complex viscosity of HPMC solutions containing actatate Na and mesilate Na were higher than HPMC alone, but were not themselves different (Student's t Test, $p < 0.05$). Benzoate Na significantly enhanced viscosity of HPMC solutions, but besilate Na was not (Student's t Test, $p < 0.05$). This might because of the relative strengths of C-C (346kJ/mol) and C-S (272 kJ/mol) bonds. Carboxyl groups have a stronger bond, may exhibit more elastic behaviour if they directly interact with the polymer. Alternatively, this may reflect differences between carboxylate and sulfonate group to disrupt water structure and dehydrate the gel.

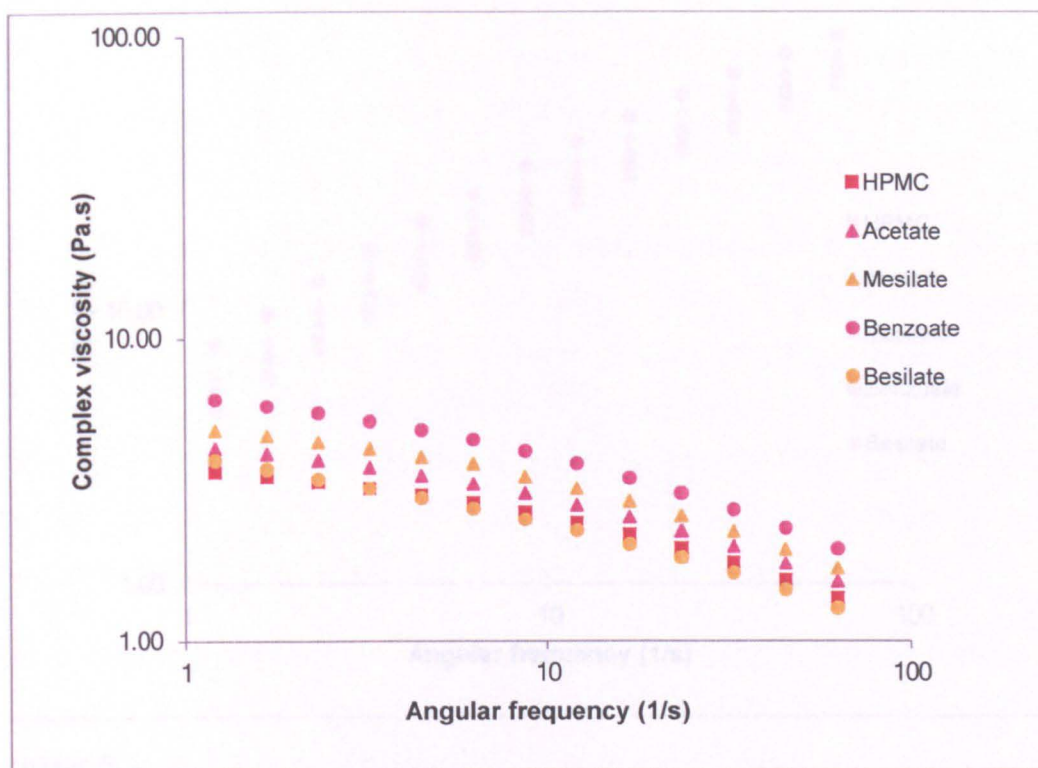
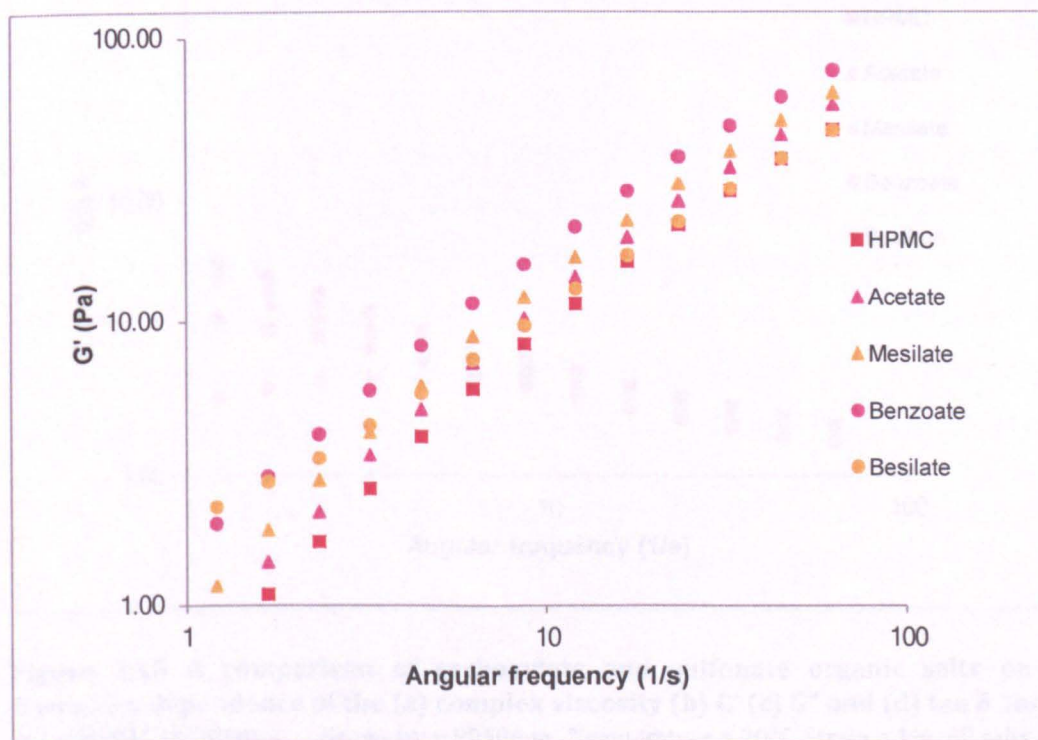
Figure 3.15(b) and (c) show the frequency dependence of the storage modulus (G') and the loss modulus (G''). These mechanical moduli were slightly increased by adding actatate Na and mesilate Na. G' was increased at low frequencies by besilate Na, but G' and G'' of HPMC solutions were increased at all frequencies by benzoate Na. This suggests that aromatic organic salts had more potential to enhance the elastic properties of HPMC solutions. The aromatic compounds are known to form stacking ring structures in solution (Sindkhedkar et al 2000; Waters 2002). This might underly their ability to enhance the viscoelastic property of HPMC solutions.

Tan δ values (figure 3.15(d)) showed a corresponding tendency to move towards gel-like behaviour ($\tan\delta = 1$) but only HPMC solutions containing besilate Na showed a substantive effect, and only at low frequencies.

Samples	Rheological data at different temperatures								
	20°C			50°C			80°C		
	G'	G''	$\tan\delta$	G'	G''	$\tan\delta$	G'	G''	$\tan\delta$
2% w/w HPMC	2.02	8.43	4.18	4.38	3.92	0.90	27.1	3.01	0.11
2% w/w HPMC + 0.50M Acetate Na	3.87	12.2	3.14	41.0	4.16	0.10	112	8.37	0.07
2% w/w HPMC + 0.50M Mesilate Na	3.14	10.1	3.22	23.6	2.74	0.12	133	12.7	0.10
2% w/w HPMC + 0.50M Benzoate Na	5.39	16.6	3.07	1.61	5.68	3.52	33.1	3.20	0.10
2% w/w HPMC + 0.50M Besilate Na	2.45	9.30	3.80	0.42	3.07	7.23	19.4	1.76	0.09

Table 3.8 Rheological data of HPMC solutions (2%w/w) containing organic salts: A comparison of carboxylate and sulfonate organic salts. The data obtained from amplitude sweeps at different temperatures. These are the value at 1% strain.

(a) Complex viscosity

(b) Storage modulus, G' 

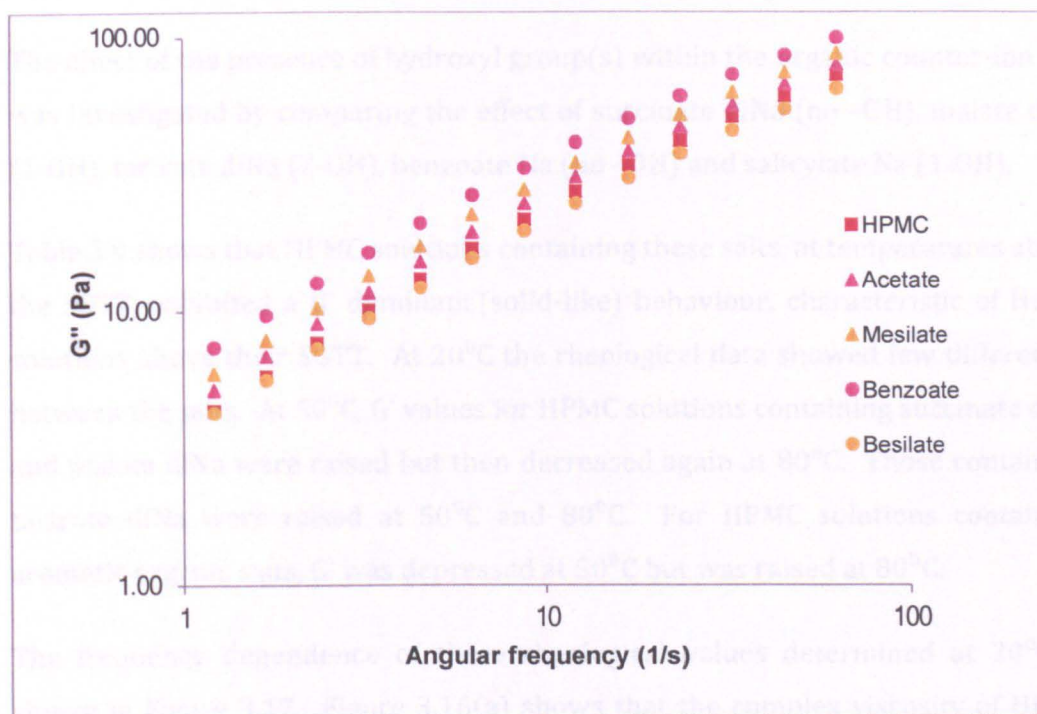
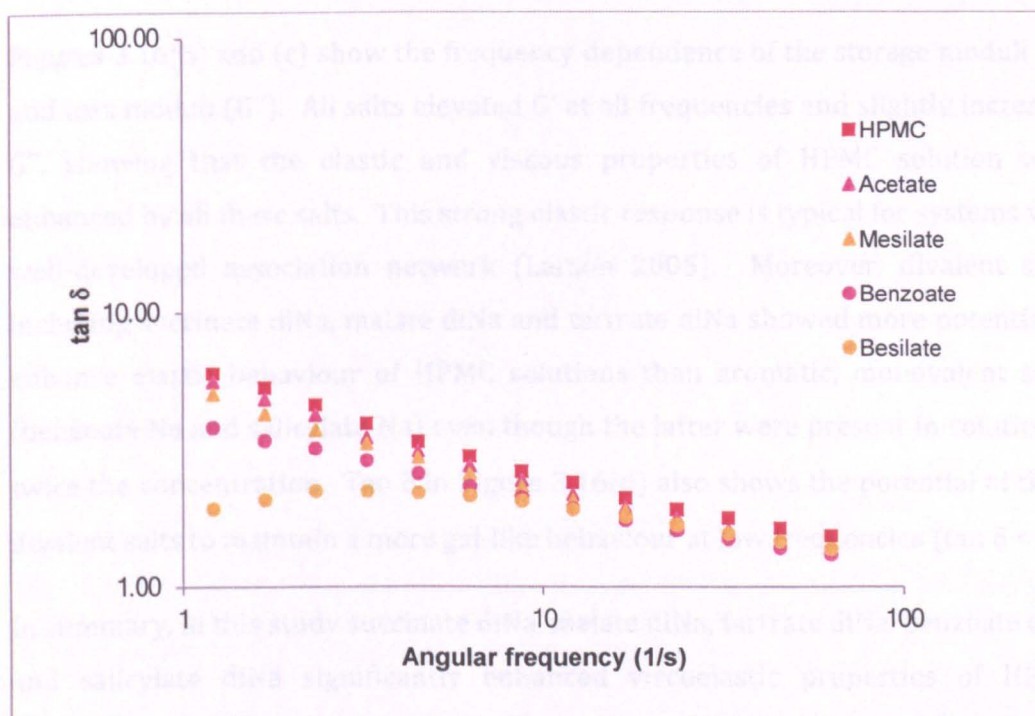
(c) Loss modulus, G'' (d) $\tan \delta$ 

Figure 3.15 A comparison of carboxylate and sulfonate organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions. Geometry = PP50mm. Temperature = 20°C. Strain = 1%. All salts were presented at 0.5M concentration.

(d) The effect of hydroxyl group substituents

The effect of the presence of hydroxyl group(s) within the organic counter-ion salt was investigated by comparing the effect of succinate diNa (no -OH), malate diNa (1-OH), tartrate diNa (2-OH), benzoate Na (no -OH) and salicylate Na (1-OH).

Table 3.9 shows that HPMC solutions containing these salts, at temperatures above the SGTT, exhibited a G' dominant (solid-like) behaviour, characteristic of HPMC solutions above their SGTT. At 20°C the rheological data showed few differences between the salts. At 50°C, G' values for HPMC solutions containing succinate diNa and malate diNa were raised but then decreased again at 80°C. Those containing tartrate diNa were raised at 50°C and 80°C. For HPMC solutions containing aromatic organic salts, G' was depressed at 50°C but was raised at 80°C.

The frequency dependence of these rheological values determined at 20°C is shown in Figure 3.17. Figure 3.16(a) shows that the complex viscosity of HPMC solutions was manifestly increased by all these salts (Student's t Test, $p < 0.05$).

Figures 3.16(b) and (c) show the frequency dependence of the storage moduli (G') and loss moduli (G''). All salts elevated G' at all frequencies and slightly increased G'' , showing that the elastic and viscous properties of HPMC solution were enhanced by all these salts. This strong elastic response is typical for systems with well-developed association network (Larson 2005). Moreover, divalent salts, including succinate diNa, malate diNa and tartrate diNa showed more potential to enhance elastic behaviour of HPMC solutions than aromatic, monovalent salts, (benzoate Na and salicylate Na) even though the latter were present in solution at twice the concentration. $\tan \delta$ in Figure 3.16(d) also shows the potential of these divalent salts to maintain a more gel-like behaviour at low frequencies ($\tan \delta < 1$).

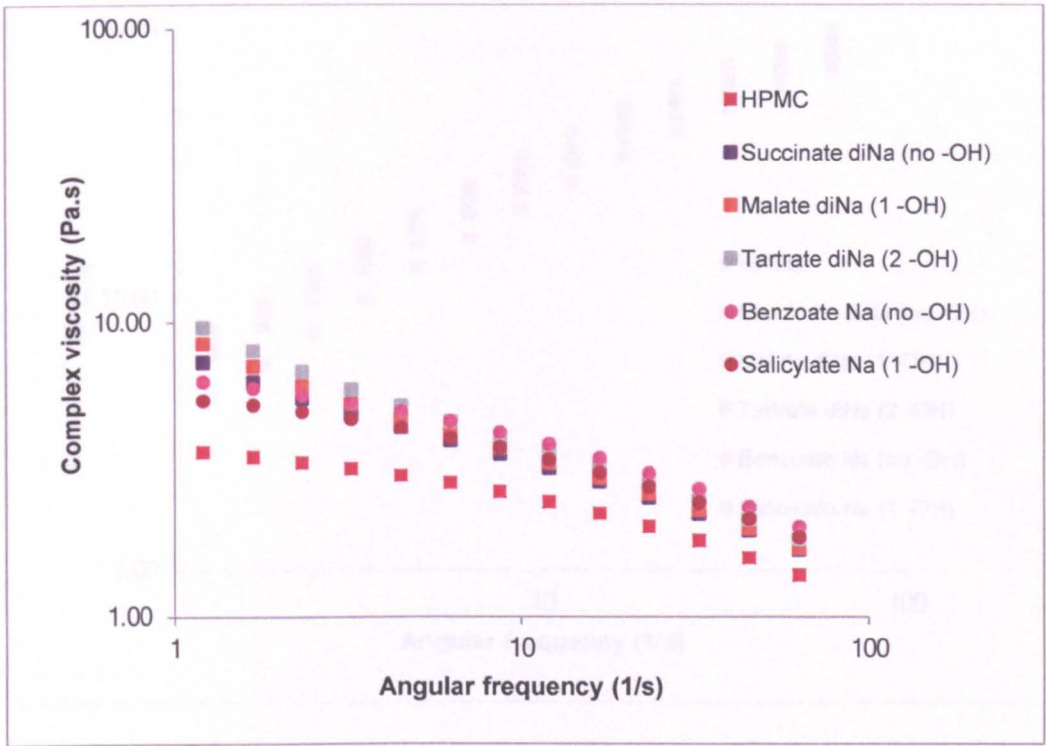
In summary, in this study succinate diNa, malate diNa, tartrate diNa, benzoate diNa and salicylate diNa significantly enhanced viscoelastic properties of HPMC, suggesting their potential to induce polymer association. However, the different hydroxyl group substituents did not affect their potential to modulate HPMC viscoelasticity.

Although the aromatic organic salts show higher degree of the effect than aliphatic organic salts as mentioned in the last section, the divalent salts still exhibited the greater effect. These results supported the hypothesis that divalent salts have more potential to enhance both elastic and viscous properties of HPMC, and greater potential to move towards gel-like behaviour at low frequencies.

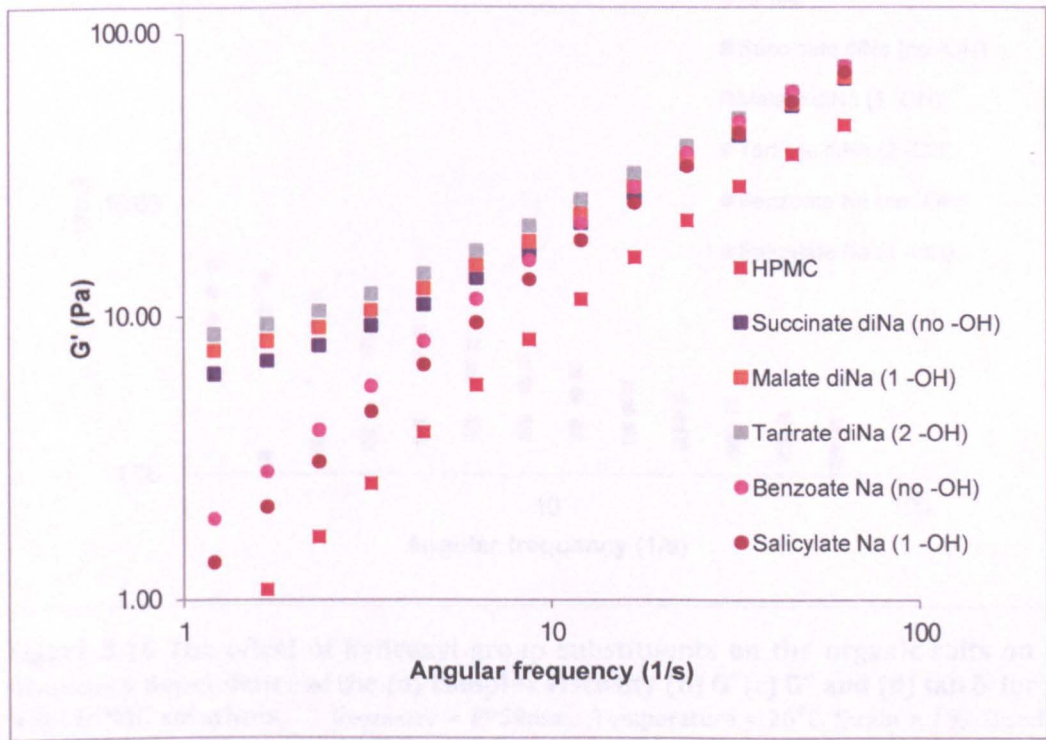
Samples	Rheological data at different temperatures								
	20°C			50°C			80°C		
	G'	G''	tanδ	G'	G''	tanδ	G'	G''	tanδ
2% w/w HPMC	2.02	8.43	4.18	4.38	3.92	0.90	27.1	3.01	0.11
2% w/w HPMC + 0.25M Succinate diNa (no -OH)	4.10	12.0	2.92	149	8.07	0.05	16.8	2.84	0.17
2% w/w HPMC + 0.25M Malate diNa (1 -OH)	6.43	13.1	2.03	183	9.20	0.05	31.2	3.87	0.12
2% w/w HPMC + 0.25M Tartrate diNa (2 -OH)	5.50	13.6	2.47	22.0	2.91	0.13	23.1	2.98	0.13
2% w/w HPMC + 0.50M Benzoate Na (no -OH)	5.39	16.6	3.07	1.61	5.68	3.52	33.1	3.20	0.10
2% w/w HPMC + 0.50M Salicylate Na (1 -OH)	5.11	15.4	3.01	0.89	5.22	5.86	6.77	2.69	0.40

Table 3.9 Rheological data of HPMC solutions (2%w/w) containing organic salts: the effect of hydroxyl group substituents. The data obtained from amplitude sweeps at different temperatures. These are the value at 1% strain

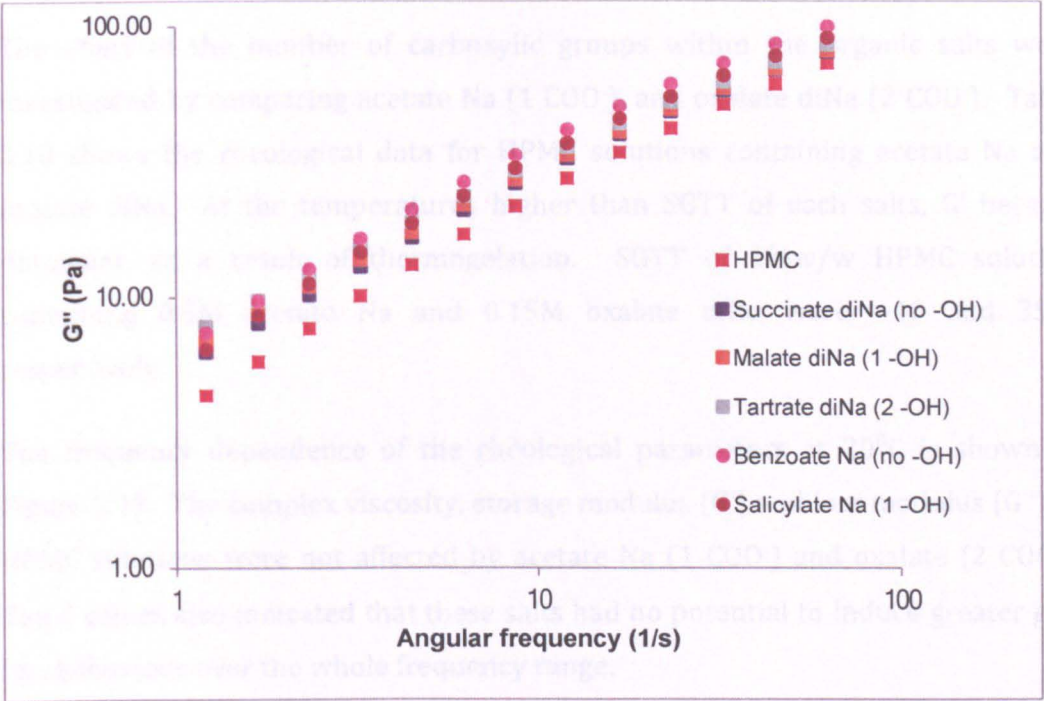
(a) Complex viscosity



(b) Storage modulus, G'



(c) Loss modulus, G''



(d) $\tan \delta$

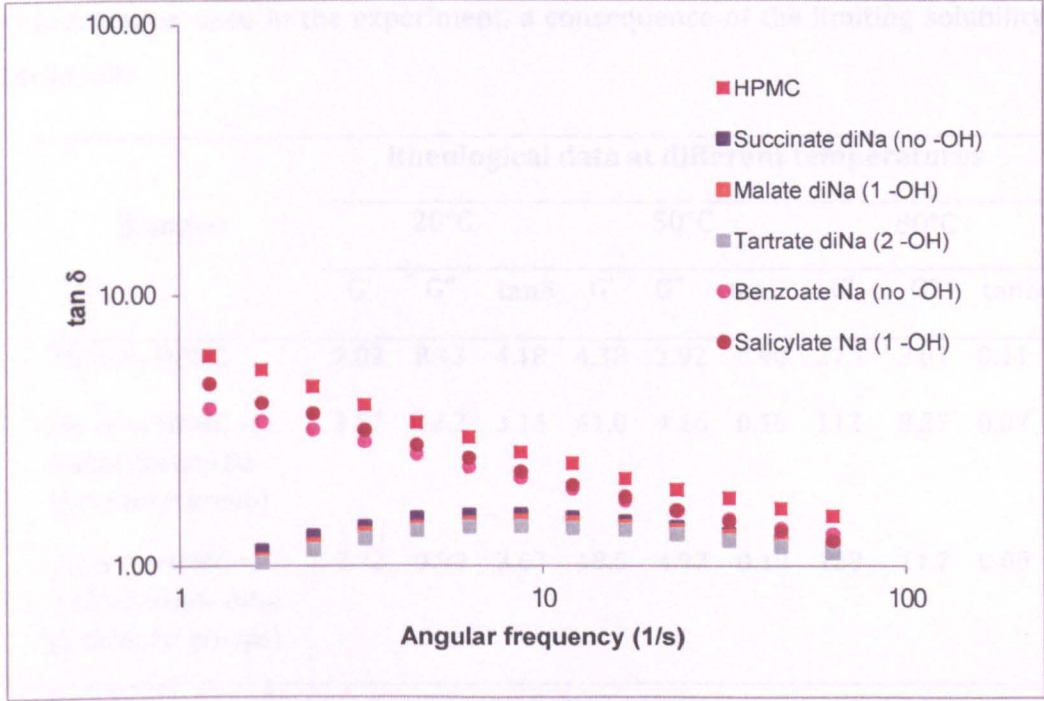


Figure 3.16 The effect of hydroxyl group substituents on the organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions. Geometry = PP50mm. Temperature = 20°C. Strain = 1%. Disodium salts (succinate, malate and tartrate) were presented at 0.25M concentration. Monosodium salts (benzoate and salicylate) were presented at 0.5M concentration.

(e) The number of carboxylic groups within counter-ion

The effect of the number of carboxylic groups within the organic salts were investigated by comparing acetate Na (1 COO⁻), and oxalate diNa (2 COO⁻). Table 3.10 shows the rheological data for HPMC solutions containing acetate Na and oxalate diNa. At the temperatures higher than SGTT of each salts, G' became dominant, as a result of thermogelation. SGTT of 1%w/w HPMC solution containing 0.5M acetate Na and 0.15M oxalate diNa were ~40 and 35°C respectively.

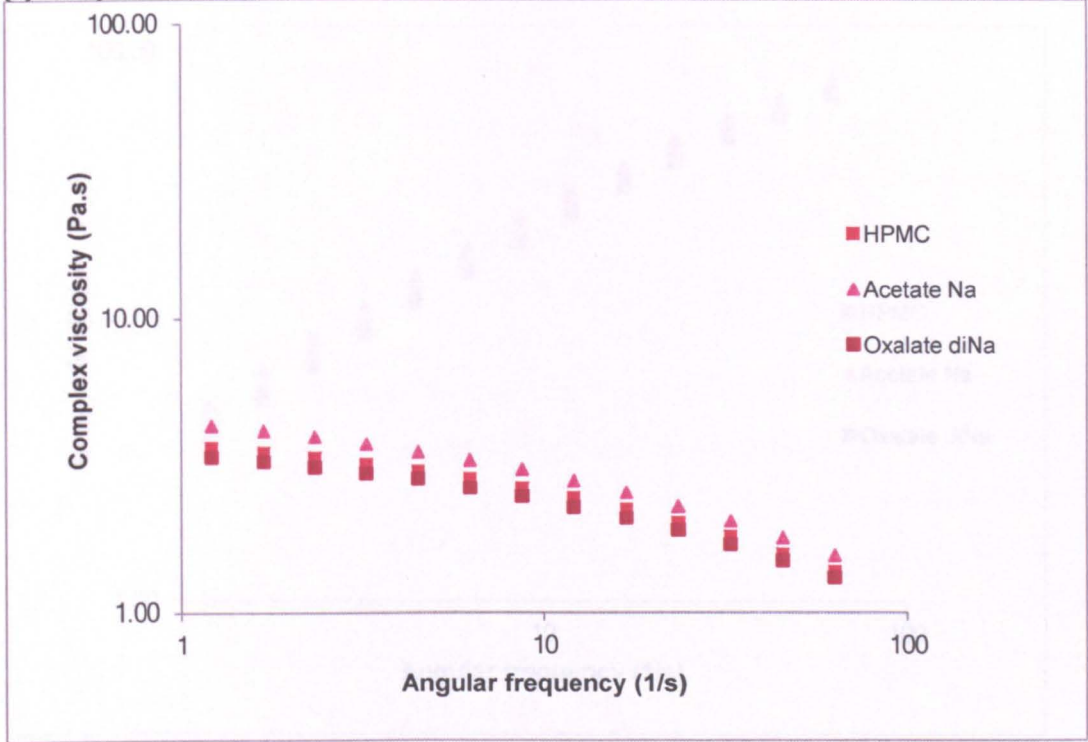
The frequency dependence of the rheological parameters at 20°C is shown in Figure 3.17. The complex viscosity, storage modulus (G') and loss modulus (G'') of HPMC solutions were not affected by acetate Na (1 COO⁻) and oxalate (2 COO⁻). Tan δ values also indicated that these salts had no potential to induce greater gel-like behaviour over the whole frequency range.

The comparison in this section was not ideal because of the different concentration used in the experiment, a consequence of the limiting solubility of these salts.

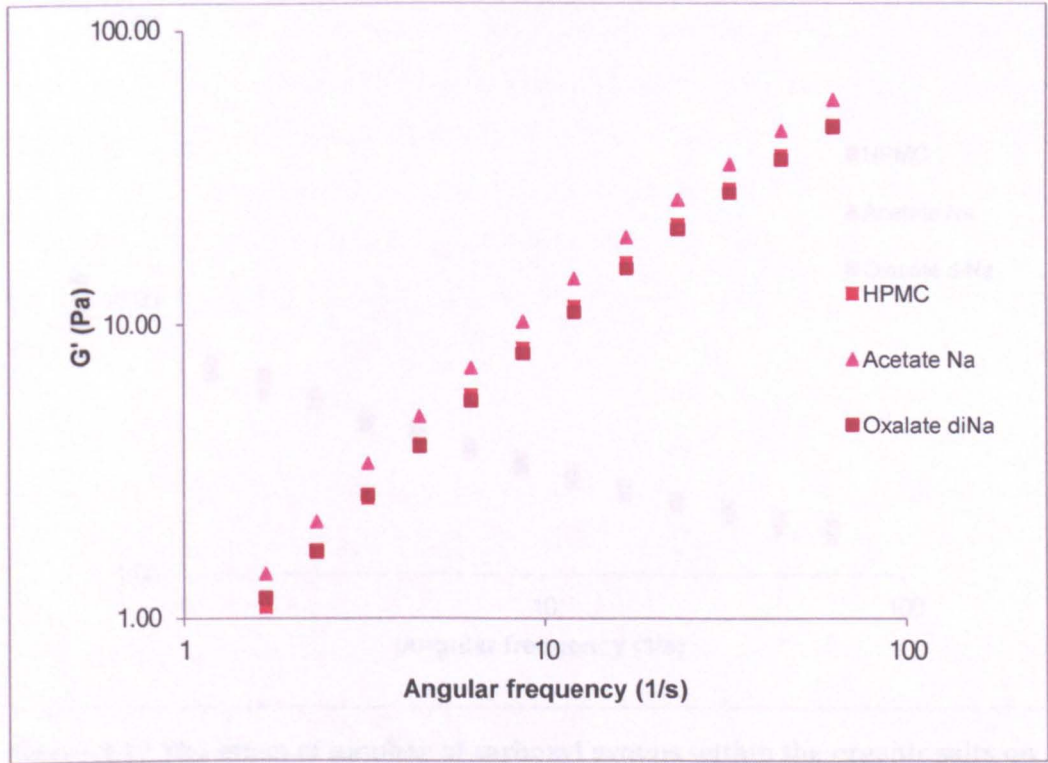
Samples	Rheological data at different temperatures								
	20°C			50°C			80°C		
	G'	G''	tanδ	G'	G''	tanδ	G'	G''	tanδ
2% w/w HPMC	2.02	8.43	4.18	4.38	3.92	0.90	27.1	3.01	0.11
2% w/w HPMC + 0.50M Acetate Na (1 carboxyl group)	3.87	12.2	3.14	41.0	4.16	0.10	112	8.37	0.07
2% w/w HPMC + 0.15M Oxalate diNa (2 carboxyl groups)	2.72	9.99	3.67	48.5	4.97	0.10	128	11.7	0.09

Table 3.10 Rheological data of HPMC solutions (2%w/w) containing organic salts: the effect of number of carboxyl groups. The data obtained from an amplitude sweeps at different temperatures. These are at 1% strain.

(a) Complex viscosity



(b) Storage modulus, G'



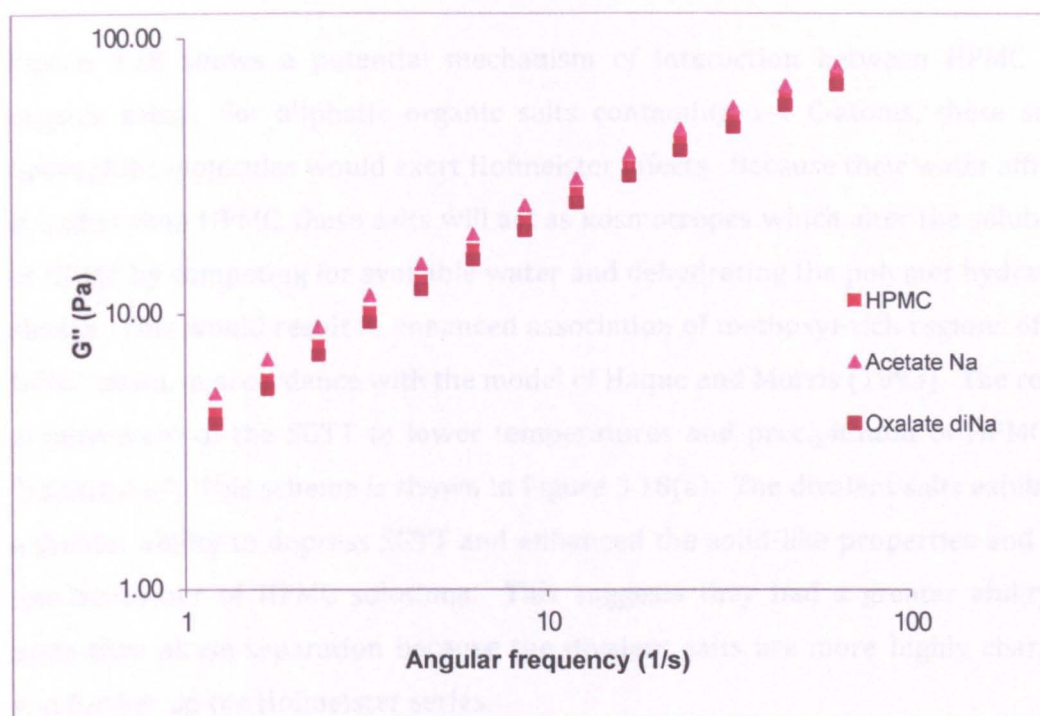
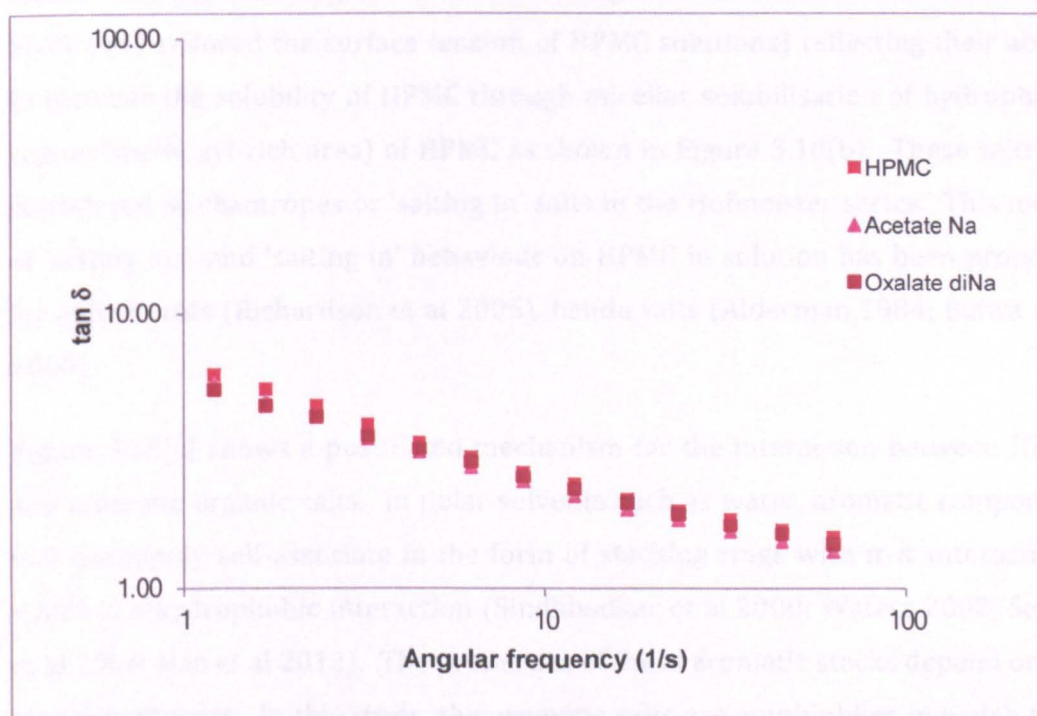
(c) Loss modulus, G'' (d) $\tan \delta$ 

Figure 3.17 The effect of number of carboxyl groups within the organic salts on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2% w/w HPMC solutions. Geometry = PP50mm. Temperature = 20°C. Strain = 1%. Acetate Na and oxalate diNa were presented at 0.5M and 0.15M concentration respectively.

3.5.4 The interaction between organic salts and HPMC

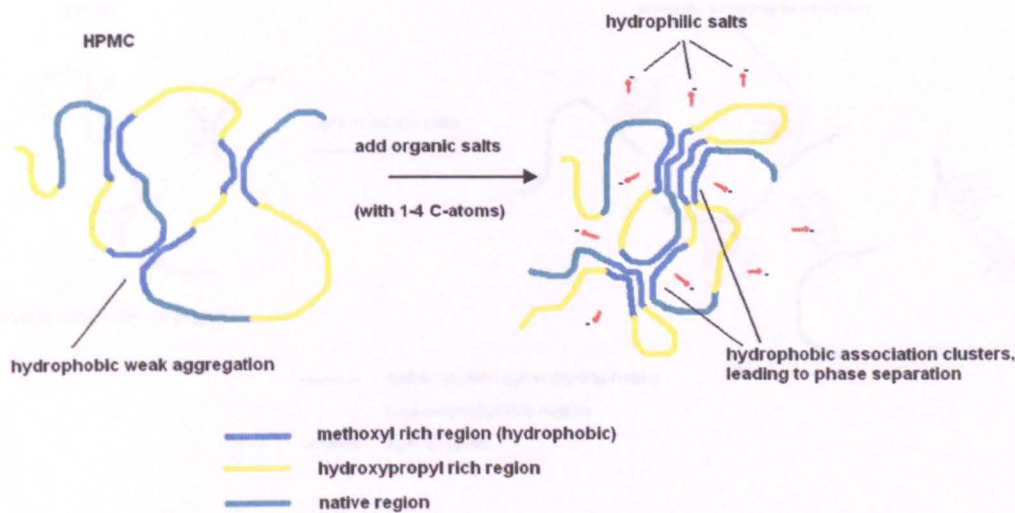
Figure 3.18 shows a potential mechanism of interaction between HPMC and organic salts. For aliphatic organic salts containing 1-4 C-atoms, these small hydrophilic molecules would exert Hofmeister effects. Because their water affinity is higher than HPMC, these salts will act as kosmotropes which alter the solubility of HPMC by competing for available water and dehydrating the polymer hydration sheath. This would result in enhanced association of methoxyl-rich regions of the HPMC chain, in accordance with the model of Haque and Morris (1993). The result is movement of the SGTT to lower temperatures and precipitation of HPMC by “salting out”. This scheme is shown in Figure 3.18(a). The divalent salts exhibited a greater ability to depress SGTT and enhanced the solid-like properties and gel-like behaviour of HPMC solutions. This suggests they had a greater ability to potentiate phase separation because the divalent salts are more highly charged, and further up the Hofmeister series.

Meanwhile, aliphatic organic salts containing over 6 C-atoms which increased SGTT (and reduced the surface tension of HPMC solutions) reflecting their ability to increase the solubility of HPMC through micellar solubilisation of hydrophobic region (methoxyl-rich area) of HPMC as shown in Figure 3.18(b). These salts are considered as chaotropes or ‘salting in’ salts in the Hofmeister series. This model of ‘salting out’ and ‘salting in’ behaviour on HPMC in solution has been proposed for amino acids (Richardson et al 2006), halide salts (Alderman 1984; Bajwa et al 2006).

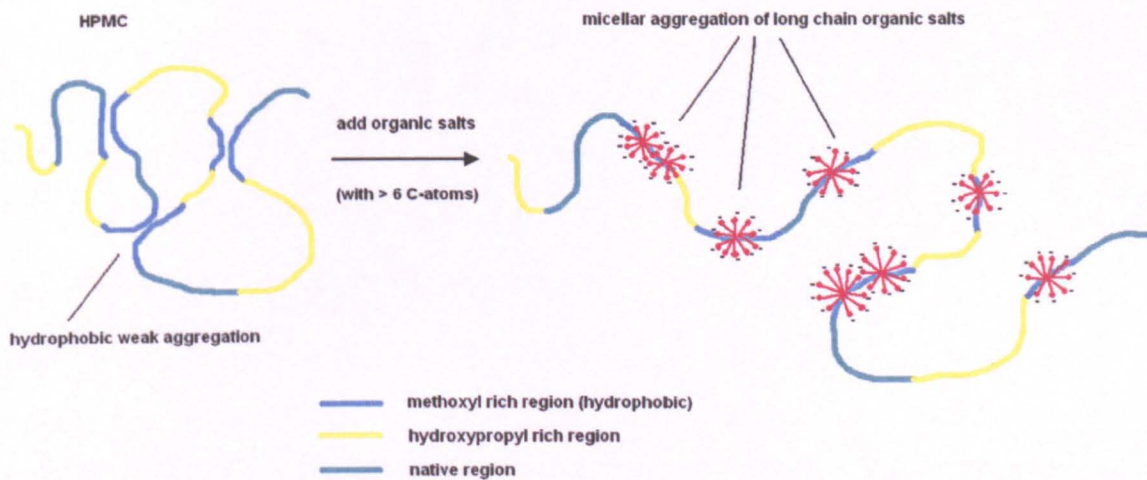
Figure 3.18(c) shows a postulated mechanism for the interaction between HPMC and aromatic organic salts. In polar solvents such as water, aromatic compounds will commonly self-associate in the form of stacking rings with π - π interactions, which is a hydrophobic interaction (Sindkhedkar et al 2000; Waters 2002; Sasaki et al 2006; Hao et al 2012). The properties of these aromatic stacks depend on the ring substituents. In this study, the aromatic salts are amphiphiles in which their aromatic stacking rings are the hydrophobic part, and the carboxylic and sulfonic groups are the hydrophilic part. The aromatic compounds consist of an anionic

group and a hydrophobic aromatic ring or ring system can induce a π -stack-type aggregation are (also categorised as hydrotropes) a configuration which can considerably enhance the aqueous solubility of organic substances if present at a sufficient concentration (Balasubramanian et al 1989; Sindkhedkar et al 2000; Matero 2002; Waters 2002; Sasaki et al 2006; Desai & Parikh 2009; Hao et al 2012). In this study, these aromatic salts which elevated SGTT and enhanced elastic behaviour of HPMC solutions might interact directly with HPMC by solubilising the hydrophobic regions of the HPMC polymer, by their stacking aggregation and amphipathic characteristics. Richardson et al (2006) also found the same effects occurred with aromatic amino acids. In addition the hydrophobic regions may become negatively charged as a result of solubilisation and absorption of the aromatic salts. These regions of negative charge would repel each other, straightening and extending the polymer chain, making the solution more viscous and gel-like entanglements more frequent. This might result in a rise of G' and G'' . In the case of the small aliphatic molecules, those higher up the Hofmeister series may give rise to denser gels (with higher G' and G'' as shown by succinate and fumarate) as a result of a greater ability to dehydrate the theme-gelled polymer.

(a)



(b)



(c)

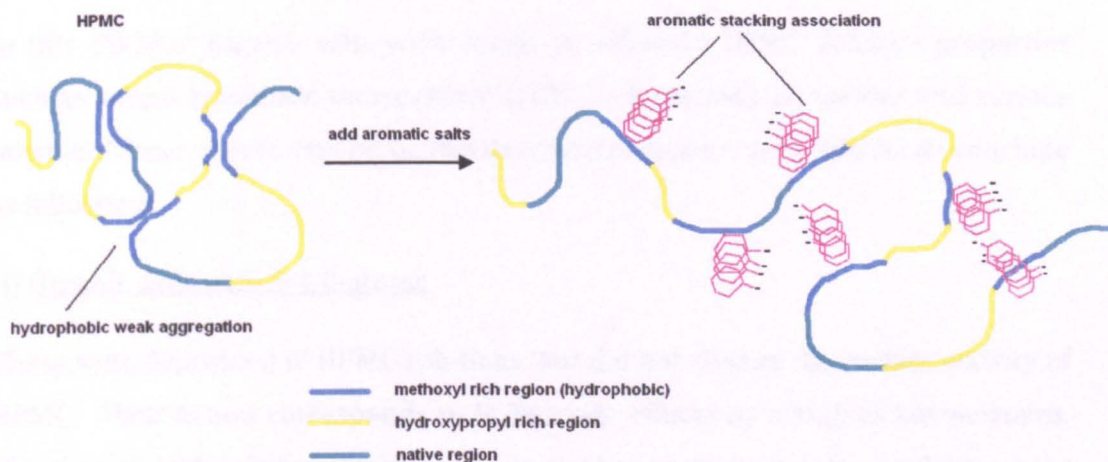


Figure 3.18 Illustration of the postulated mechanisms between HPMC and organic salts containing (a) 1-4 C-atoms (b) over 6 C-atoms and (c) containing an aromatic ring.

3.6 Conclusions

In this chapter, organic salts were found to influence HPMC solution properties such as sol:gel transition temperature (SGTT), viscoelastic behaviour and surface tension. These effects depend on the structure of organic salts which can conclude as following:

(i) Organic salts with 1-4 C-atoms

These salts depressed of HPMC solutions, but did not change the surface activity of HPMC. Their action corresponds to Hofmeister effects by acting as kosmotropes. These small hydrophilic molecules are thought to compete for the available water and remove water from the polymer hydration sheath of HPMC, and hence cause HPMC precipitation ("salting out"). The rheological studies also provided the evidence that divalent salts had potential to enhance the solid-like properties of HPMC solution both below and above the SGTT.

(ii) Organic salts with over 6 C-atoms

These salts elevated SGTT and reduced the surface tension of HPMC solutions. These results provide a hypothesis that these salts might act as chaotropes of the Hofmeister series, and possibly solubilise the hydrophobic regions of HPMC through micellar solubilisation.

(iii) Organic salts containing an aromatic group

These salts elevated SGTT of HPMC solutions, but showed no effect on the surface activity of HPMC. The rheological studies provided the evidence that they had potential to enhance the viscoelastic behaviour of HPMC solutions. These support a hypothesis that the aromatic organic salts might act as hydrotropes and solubilise the hydrophobic regions of HPMC by stack-type aggregation and amphiphilicity.

All the investigations in this chapter suggest that the organic salts used as counter-ions might affect the gel layer formation of HPMC matrices, so that these salts might be one factor that we should consider in HPMC matrices formulation. In next chapter, the effect of these organic salts on HPMC matrices will be investigated.

Chapter 4

The Effect of Organic salts on HPMC Matrices

4.1 Rationale

Previous chapters have shown that some organic salts used as drug counter-ions, can affect the properties of HPMC in solution. This suggests that they may also have an influence on the gel layer of HPMC matrices. In this chapter, the effect of these organic salts on matrices will be investigated, with the intention that this understanding may be useful in the future formulation of HPMC matrices.

4.2 Introduction

The effect of many additives on the extended release performance of HPMC has been studied. Soluble or insoluble diluents, and anionic surfactants for example may influence drug release rates (Lapidus & Lordi 1968; Daly et al 1984) whereas magnesium stearate did not affect the release rates of promethazine (Ford et al 1985b). The solubility and particle size of drug may also alter the release rate of HPMC matrices (Ford et al 1985a; Ford et al 1985b; Ford et al 1987). It has been postulated that highly soluble drugs and excipients can act as pore formers, with micro-cavities making the gel structure more porous and physically weaker, leading to increased drug release rates (Yang & Fassihi 1997). Sheu et al (1992) found that the release rate of diclofenac sodium can be retarded by the use of sodium chloride, which salted out diclofenac sodium, and resulted in a lower dissolution rate. Diclofenac sodium matrices using HPMC and carboxypolymer mixtures as the controlled release polymer, studied by Bravo et al (2004), showed

how more rapid release occurred as the carboxypolymer ratio within the matrices increased. This could be a hydration or a molecular weight induced change, but these matrices were also pH dependent because the carboxypolymer needed to be ionized to be able to interact with HPMC to control the drug release.

Tablet diluents can have significant effects. It has been reported that microcrystalline cellulose (MCC) can change the dissolution profile by accentuating the initial burst effect, whilst non-swellable insoluble fillers, for example, dicalcium phosphate, completely destroy sustained release properties of HPMC matrix tablets with a low polymer formulation (Alderman 1984). The use of partially gelatinized maize starch, Starch 1500®, in chlorpheniramine maleate and theophylline matrices has been found to retard drug release rate because of a potential synergistic interaction between Starch 1500 and HPMC, whilst, MCC and spray-dried lactose were found in the same formulations to accelerate drug release (Levina & Rajabi-Siahboomi 2004).

The effect of internal buffering agents such as tris(hydroxymethyl) aminomethane (THAM, TRIS) and sodium citrate on HPMC matrices has been shown to accelerate release of the weak acid drug in both pH 1.2 and 7.5 media (Pygall et al 2009; Pygall et al 2010).

High levels of ionic salts, particularly multivalent ions, can cause precipitation of HPMC leading to premature drug release (Alderman 1984). The ionic strength of electrolytes in a dissolution media can affect the drug release rate of HPMC matrices and an ionic strength of approximately 0.5mol/L or greater in the dissolution media can cause the burst release of the matrices (Xu et al 2006).

4.3 Chapter Aims and Objectives

In this chapter, the effect of selected organic salts, which are used as drug counterions, on HPMC matrix properties are investigated with respect to (i) organic salt chain length and (ii) organic salt structure activity relationship. The study in matrices aimed to explore the influence of these organic salts on the drug release from HPMC matrices both with and without diluents incorporating into the tablet.

In particular, the experimental work in this chapter, investigates the effect of organic species on the extended release performance of HPMC matrices.

In the end, the correlation between the effect of these organic salts on the drug release performance of HPMC matrices (from this Chapter) and on the sol:gel transition temperature (from Chapter 3 Section 3.5.1) of HPMC solutions was determined.

4.4 Materials and Methods

4.4.1 Organic salts

4.4.1.1 A homologous series

The simplest series of organic counter-ions was chosen from Table 1.3 in order to study the relationship between aliphatic chain length and ion effects on HPMC. The homologous series of aliphatic organic sodium salts containing a 1-carboxylic group are shown in Table 3.1 and the source and batch numbers of these materials are documented in Appendix 1.

4.4.1.2 The relative groups

The organic salts shown in Table 1.3 were selected and categorised according to their functional groups and structural relationships. In this chapter, the effect of these groups on HPMC were studied by comparing salts with (a) geometric isomerism (b) degree of ionisation (c) different acid functional groups (carboxyl and sulfonic acids) (d) the presence of hydroxyl group(s) and (e) the number of carboxyl groups. These organic salts are listed in Chapter 3 (Table 3.2) and the source and batch numbers of these materials are documented in Appendix 1.

4.4.2 HPMC

HPMC USP Type 2910 (Methocel™ E4M CR Premium EP/USP) and HPMC USP Type 2208 (Methocel™ K4M CR Premium EP/USP) were used in this study. Full details of these materials are given in Appendix 1.

4.4.3 Manufacture of matrix tablets

Matrix tablets weighing 250 ± 5 mg were manufactured using a Manesty F3 single punch tablet press (Manesty, Liverpool, UK) at a compression pressure of 160MPa (within the linear range of compression pressure-hardness profile), using 8 mm flat-faced punches (I Holland, Nottingham, UK) as described in section 2.2.7. The formulations of HPMC matrices used in this chapter are shown in Table 4.1, 4.2 and 4.3. For the study of the effect of amount of organic salts, tablets were

prepared containing by weight, a high amount of organic salts (60%w/w) without diluents and a low amount (10%w/w) of organic salts with diluents (Table 4.1). In the study of the effects of different diluents, tablets were prepared with a diluent of high solubility (dextrose), an insoluble diluent (microcrystalline cellulose), a diluent of intermediate solubility (partially pre-gelatinized starch) and the 50:50 mixtures of each (Table 4.2). The effect of diluents in the presence of an organic salt, succinate diNa, was also studied (Table 4.3(a)) which Table 4.3(b) shows the control formulations for table 4.3(a) with C_H, C_I, C_J, C_K and C_L being the controls for H, I, J, K and L respectively. Different types of HPMC, including HPMC E4M, HPMC E4M (63-90µm fraction) and HPMC K4M were used in the study for the effect of diluents.

Note: Compression pressure-hardness profiles for matrix tablets containing each organic salt were obtained, in order to determine the appropriate compression pressure. A compression pressure of 160 MPa was chosen because it was within the linear compression range for all organic salt formulations (Data not shown).

Ingredients	Weight Composition (%w/w)		
	A	B	Control
Caffeine anhydrous ^a	10.0	10.0	10.0
HPMC	30.0	30.0	30.0
Organic salt ^b	60.0	10.0	-
Dextrose	-	50.0	60.0

Table 4.1 The formulation of HPMC matrix tablets containing (A) high amounts of salts without diluents (B) low amounts of the salts with diluents used in this chapter.

^a <125 μ m sieve fraction. ^b selected organic salts as described in section 4.4.1. Full details of all materials are provided in Appendix 1.

Ingredients	Grade/ Type	Weight Composition (%w/w)				
		C	D	E	F	G
Caffeine anhydrous ^a	Analytical grade	10.0	10.0	10.0	10.0	10.0
HPMC	Methocel™ E4M CR/ Methocel™ E4M CR (63-90 μ m fraction)/ Methocel™ K4M CR	30.0	30.0	30.0	30.0	30.0
Dextrose	Meritab®	60.0	-	30.0	-	30.0
Pre-gelatinised Starch	Starch 1500®	-	60.0	30.0	-	-
Microcrystalline Cellulose (MCC)	Avicel PH102	-	-	-	60.0	30.0

Table 4.2 The formulation of HPMC matrix tablets used in the study of the effect of diluents on HPMC matrices.

^a <125 μ m sieve fraction. Full details of all materials are provided in Appendix 1.

(a) Formulation of matrices containing an organic salt

Ingredients	Grade/ Type	Weight Composition (%w/w)				
		H	I	J	K	L
Caffeine anhydrous ^a	Analytical grade	10.0	10.0	10.0	10.0	10.0
HPMC	Methocel™ E4M CR	30.0	30.0	30.0	30.0	30.0
Succinate disodium	-	10.0	10.0	10.0	10.0	10.0
Dextrose	Meritab®	50.0	-	25.0	-	25.0
Pre-gelatinised Starch	Starch 1500®	-	50.0	25.0	-	-
Microcrystalline Cellulose (MCC)	Avicel PH102	-	-	-	50.0	25.0

(b) Control formulations

Ingredients	Grade/ Type	Weight Composition (%w/w)				
		C _H	C _I	C _J	C _K	C _L
Caffeine anhydrous ^a	Analytical grade	10.0	10.0	10.0	10.0	10.0
HPMC	Methocel™ E4M CR	30.0	30.0	30.0	30.0	30.0
Dextrose	Meritab®	60.0	10.0	35.0	10.0	35.0
Pre-gelatinized Starch	Starch 1500®	-	50.0	25.0	-	-
Microcrystalline Cellulose (MCC)	Avicel PH102	-	-	-	50.0	25.0

Table 4.3 The formulation of HPMC matrix tablets used in the study of the effect of diluents on HPMC matrices containing disodium succinate.

^a <125 μ m sieve fraction. Full details of all materials are provided in Appendix 1.

4.4.4 Dissolution determination

Drug release profiles of HPMC matrices were determined at $37\pm0.5^{\circ}\text{C}$ in 900ml of degassed media using USP dissolution apparatus I (basket) at 100rpm (Dissolutest, Prolabo, France). The main dissolution media used was deionized water but sodium chloride (NaCl), Potassium chloride (KCl), and simulated gastric fluid USP without enzymes (SGF) were also used in this chapter. Full details of the dissolution method are provided in Section 2.2.8.

4.4.4.1 The preparation of dissolution media

To prepare 0.154M NaCl solution, 54.00g of NaCl was weighed and completely dissolved in a small amount of water, and then made up to 6L with deionised water. To prepare a 0.154M KCl, 68.89g of KCl was weighed and completely dissolved in a small amount of water, and then made up to 6L with water. Simulated gastric fluid (SGF) without enzymes was prepared according to the USP 29. 1L of SGF was prepared by dissolving 2g of sodium chloride in a small amount of water, and then adding the appropriated amount of hydrochloric acid to achieve pH 1.2, and finally made up to 1L with water. All media were degassed by helium sparging for at least 20 minutes prior to use. The reagents and the quality and source of the deionised water are described in Appendix 1.

4.4.5 Statistical analysis

Statistical differences between drug release profiles were determined using a one-way ANOVA (JMP 7 software, SAS Institute Inc., Cary, NC). A *p* value of less than 0.05 was considered statistically significant.

The drug release profiles were also compared by using the difference factor (f_1) and similarity factor (f_2). The difference factor (f_1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error as shown in equation 4.1. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_1 = \{[\sum_{t=1}^n |R_t - T_t|] / [\sum_{t=1}^n R_t]\} * 100 \quad \text{Equation 4.1}$$

$$f_2 = 50 * \log\{[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} * 100\} \quad \text{Equation 4.2}$$

where n is the number of time points, R_t is the dissolution value of the reference batch at time t , and T_t is the dissolution value of the test batch at time t .

If f_1 values are close to 0 (generally 0-15) and f_2 values are close to 100 (generally 50-100), the two curves are considered similar or equivalent. On the other hand if f_1 values are more than 15 and f_2 values are less than 50, the two curves are considered different (US FDA; Shah 1998; Pillay & Fassihi 1998; Gohel et al 2005, Wadher et al 2011).

4.4.6 Photography of hydrating HPMC matrices

Hydrated matrix tablets taken from the dissolution determination were collected to image at 0min, 10 min, 1hour, and 8hours using a Celestron handheld digital microscope (Celestron®, Torrance, CA, USA) and a digital camera (canon®ixus55, Japan)

4.5 Results and Discussion

4.5.1 The selection of the dissolution media

Four dissolution media (deionised water, 0.15M NaCl, 0.15M KCl and simulated gastric fluid USP without enzymes (SGF)) were used in this study. To isolate the effect of the organic salt on the HPMC matrix tablet, these tablets contained only an organic salt, HPMC and a model drug (formulation A in Table 4.1). Dissolution tests of HPMC matrices containing acetate Na, pentanoate Na, or octanoate Na were conducted in these four dissolution media using apparatus I at 100 rpm and 37°C. The release profiles are shown in Figure 4.1. Matrices incorporating each salt exhibited significantly different drug release profiles in every dissolution media ($p < 0.05$, one-way ANOVA) and the rank order of drug release was always :

acetate (C2) > pentanoate (C5) > octanoate (C8)
 highest ←———— dissolution rate ————— lowest

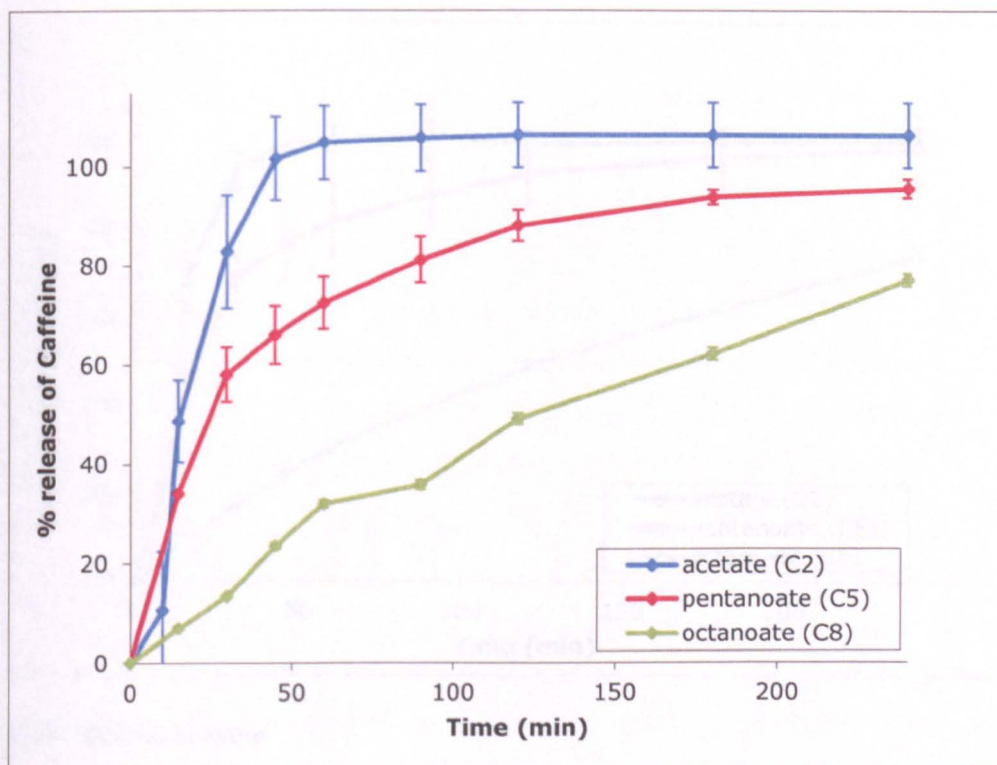
However, the difference (f_1) and similarity factors (f_2) also highlighted differences in different media (Table 4.4). Water showed the greatest difference between the salts.

As the aim of this thesis is to investigate the influence of the organic salts on drug release from HPMC matrices, it was decided that ionic strength should be controlled as least as possible. A simple two component test medium (water and salts component) would best facilitate the identification of potential interactions between the salts and the model HPMC matrix. Therefore water was chosen as the main dissolution medium to be used throughout this thesis. Further details of the effect of these organic salts on HPMC matrices will be discussed in section 4.5.4.

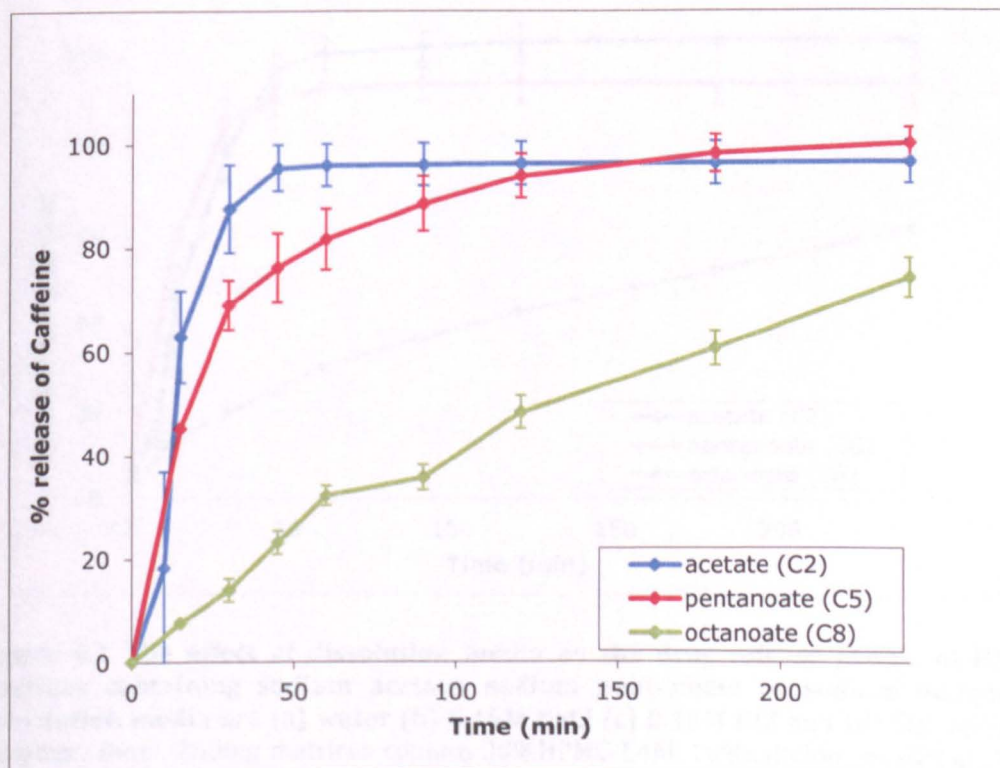
Dissolution media	f_1	f_2
Water	26.23	31.46
0.15M NaCl	16.15	41.34
0.15M KCl	21.17	34.22
SGF (without enzyme)	13.26	45.87

Table 4.4 The difference factor (f_1) and the similarity factor (f_2) between HPMC matrices containing acetate Na and pentanoate Na.

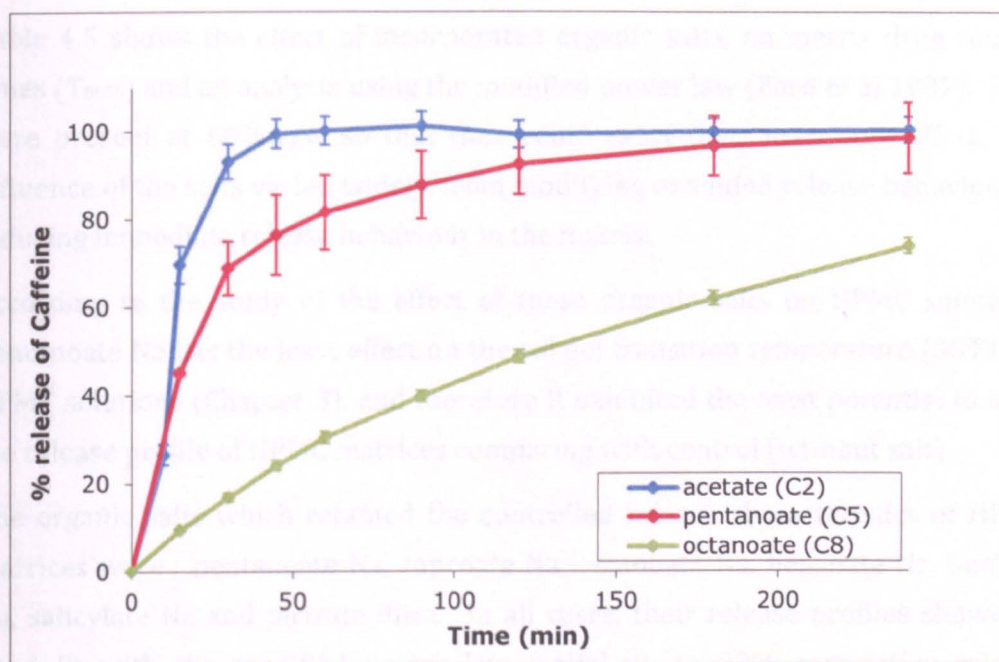
(a) water



(b) 0.15M NaCl



(c) 0.15M KCl



(d) SGF without enzyme

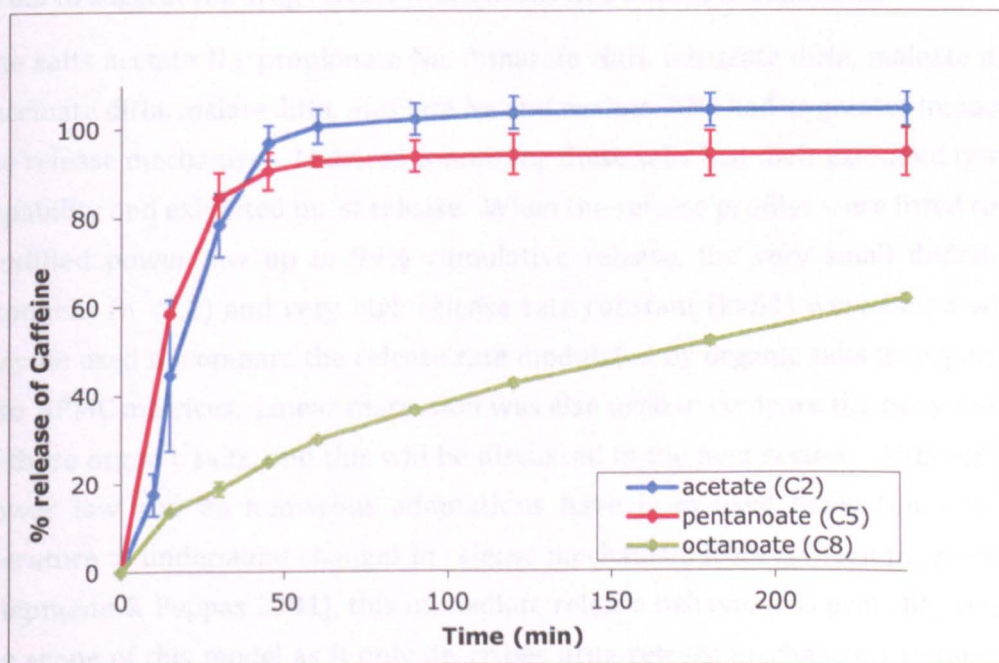


Figure 4.1 The effect of dissolution media on the drug release profile of HPMC matrices containing sodium acetate, sodium pentanoate or sodium octanoate. Dissolution media are (a) water (b) 0.15M NaCl (c) 0.15M KCl and (d) SGF without enzyme. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. USP I, 100rpm, 37°C in dissolution medium. Mean(n=3)± 1S.D.

4.5.2 The effect of 60% organic salts on drug release from HPMC matrices

Table 4.5 shows the effect of incorporated organic salts, on matrix drug release times ($T_{80\%}$) and an analysis using the modified power law (Ford et al 1987). Salts were present at 60%w/w so that they could exert their maximum effect. The influence of the salts varied widely, from modifying extended release behaviour to inducing immediate release behaviour in the matrix.

According to the study of the effect of these organic salts on HPMC solutions, pentanoate Na has the least effect on the sol:gel transition temperature (SGTT) of HPMC solutions (Chapter 3), and therefore it exhibited the least potential to alter the release profile of HPMC matrices comparing with control (without salt).

The organic salts which retained the controlled release characteristics of HPMC matrices were : pentanoate Na, caproate Na, octanoate Na, benzoate Na, besilate Na, salicylate Na and tartrate diNa. In all cases, their release profiles showed a good fit with the modified power law model up to 80% cumulative release ($r^2 > 0.99$), and the exponent (n) was within the range of 0.386-0.632, close enough to 0.5 to suggest the drug release mechanism was diffusion-dominated.

The salts acetate Na, propionate Na, fumarate NaH, fumarate diNa, maleate diNa, succinate diNa, malate diNa, mesilate Na and oxalate diNa had as greater impact on the release mechanism. Matrices containing these salts lost their extended release capability and exhibited burst release. When the release profiles were fitted to the modified power law up to 99% cumulative release, the very small diffusional exponent ($n < 0.1$) and very high release rate constant ($k > 54$) were found which may be used to compare the release rate modulated by organic salts incorporated into HPMC matrices. Linear regression was also used to compare the early release of these organic salts, and this will be discussed in the next section. Although the power law and its numerous adaptations have been used many times in the literature to understand changes in release mechanism from gel-forming matrices (Siepmann & Peppas 2001), this immediate release behaviour is probably outside the scope of this model as it only describes drug release mechanisms in terms of gel layer diffusion and erosion.

In the following sections, the effect of these organic salts on drug release is discussed in terms of structure-activity relationships.

Organic salts	$T_{80\%}$	k	n	r^2
<u>Control</u>				
No salt (dextrose used as a diluent)	178	9.58	0.419	0.9992
<u>Homologous series</u>				
Acetate Na	13	96.84 ^(a)	0.005 ^(a)	0.9378 ^(a)
Propionate Na	14	93.19 ^(a)	0.015 ^(a)	0.8948 ^(a)
Pentanoate Na	150	10.03	0.386	0.9994
Caproate Na	240	3.82	0.564	0.9990
Octanoate Na	264	2.49	0.632	0.9907
<u>Geometric isomerism</u>				
Fumarate diNa	14	90.33 ^(a)	0.022 ^(a)	0.9492 ^(a)
Maleate diNa	56	54.25 ^(c)	0.106 ^(c)	0.9742 ^(c)
<u>Ionisation</u>				
Fumarate Na H	14	86.91 ^(a)	0.032 ^(a)	0.9585 ^(a)
Fumarate diNa	14	90.33 ^(a)	0.022 ^(a)	0.9492 ^(a)
<u>Functional groups</u>				
Acetate Na	13	96.84 ^(a)	0.005 ^(a)	0.9378 ^(a)
Mesilate Na	37	61.57 ^(c)	0.088 ^(c)	0.9940 ^(c)
Benzoate Na	170	7.56	0.475	0.9989
Besilate Na	206	4.87	0.542	0.9985
<u>The presence of hydroxyl group(s)</u>				
Succinate diNa	23	78.79 ^(b)	0.062 ^(b)	0.9034 ^(b)
Malate diNa	27	64.46 ^(b)	0.114 ^(b)	0.9292 ^(b)
Tartrate diNa	89	27.13	0.251	0.9985
Benzoate Na	170	7.56	0.475	0.9989
Salicylate Na	113	9.36	0.472	0.9977
<u>The number of carboxylic groups</u>				
Acetate Na	13	96.84 ^(a)	0.005 ^(a)	0.9378 ^(a)
Oxalate diNa	12	92.77 ^(a)	0.017 ^(a)	0.9630 ^(a)

Table 4.5 The effect of 60% organic salts on drug release kinetics using the modified power law. Modified power law is described by Ford et al (1987) and was fitted up to 80% cumulative release. 8mm, 250mg matrices, 160MPa containing 30% HPMC E4M, 10% caffeine anhydrous, 60% organic salt $T_{80\%}$ is the time to 80% cumulative drug release. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient. (a) Drug release >80% within 15 min. (b) Drug release >80% within 30 min. (c) Drug release >80% within 1h. These fast release matrices were calculated up to 99% cumulative release and also evaluated by linear regression for the early release.

4.5.2.1 The effect of the C-chain length of organic salts on drug release from HPMC matrices (homologous series)

Release profiles for HPMC matrices containing a homologous series of aliphatic organic salts are shown in Figure 4.2. The release data and kinetics (extracted from Table 4.5) are shown in Table 4.6.

The release rate constant (k) and the time to 80% cumulative drug release ($T_{80\%}$) were in a rank order of C-chain length as follows:

acetate (C2) > propionate (C3) > pentanoate (C5) > caproate (C6) > octanoate (C8)

← release rate →

acetate (C2) = propionate (C3) < pentanoate (C5) < caproate (C6) < octanoate (C8)

→ $T_{80\%}$ →

These salts show the same rank order as their effects on the sol:gel transition temperature of HPMC solutions (Chapter 3). Their correlation will be discussed in section 4.5.4.

With respect to control the longer C-chain salts retarded the release from the matrix, whereas the shorter C-chain lengths accelerated drug release. If we use the same arguments derived by Richardson et al (2006) to explain the effects of amino acids on the sol:gel transition temperature, then these salts may modulate the release profiles of HPMC matrices by virtue of their hydrophobicity. The more hydrophilic salts, acetate (C2) and propionate (C3) would accelerate drug release by competing for water, in the hydration sheath of the polymer as do common anionic salts such as sulphate and phosphate. In the hydrating matrix this would result in inhibition of polymer swelling, interfering with gel layer formation, compromising the gel diffusion barrier and leading to greater liquid penetration of the matrix core. The more hydrophobic salts, caproate (C6) and octanoate (C8) would increase polymer hydration through micellar solubilisation of HPMC, making gel layer formation more rapid, and it seems, more effective as a drug retarding barrier.

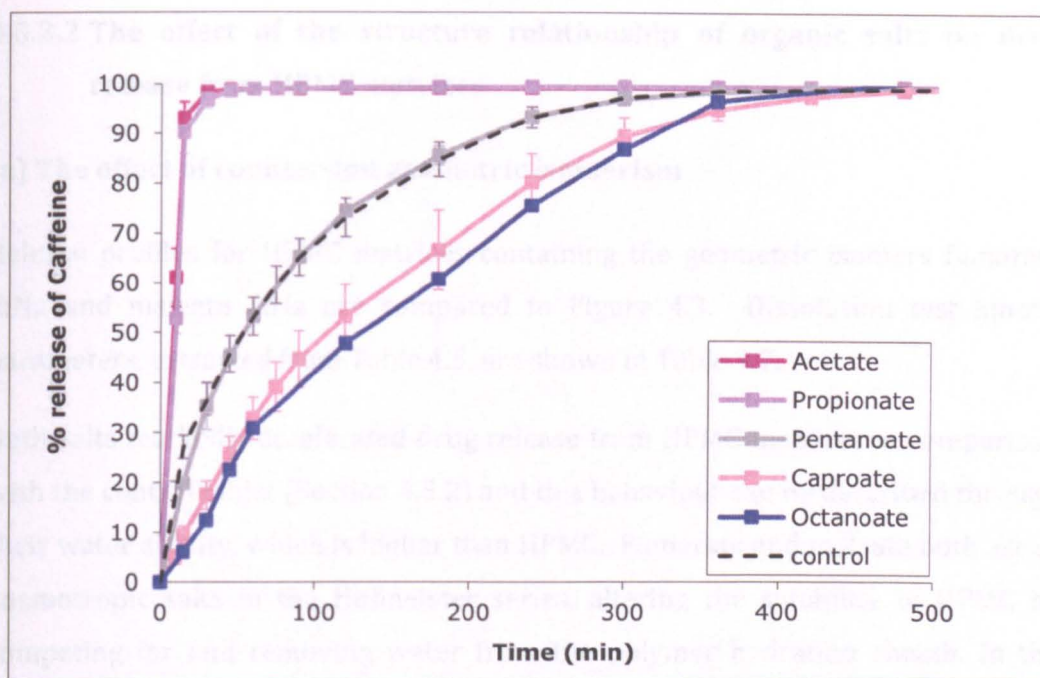


Figure 4.2 The effect of C-chain length of the organic salts on the drug release profile of HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D.

Organic salts	T _{50%}	T _{80%}	Modified power law (Ford et al 1987)			Linear regression	
			k	n	r ²	k	r
<i>Control</i>							
No salt (dextrose used as a diluent)	66	178	9.58	0.419	0.9992	1.32	0.9963
<i>Homologous series</i>							
Acetate Na	8	13	96.84(a)	0.005(a)	0.9378(a)	6.19	0.9999
Propionate Na	10	14	93.19(a)	0.015(a)	0.8948(a)	5.91	0.9958
Pentanoate Na	54	150	10.03	0.386	0.9994	1.17	0.9974
Caproate Na	109	240	3.82	0.564	0.9990	0.55	0.9984
Octanoate Na	130	264	2.44	0.638	0.9880	0.52	0.9948

Table 4.6 The effect of an aliphatic homologous series of organic salts on drug release kinetics using the modified power law and linear regression. Modified power law is fitted up to 80% cumulative release, but the fast release matrices were calculated up to 99% cumulative release. Linear regression is fitted for the early release. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. $T_{50\%}$ and $T_{80\%}$ are the time to 50% and 80% cumulative drug release respectively. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient. (a) Drug release >80% within 15 min.

4.5.2.2 The effect of the structure relationship of organic salts on drug release from HPMC matrices

(a) The effect of counter-ion geometric isomerism

Release profiles for HPMC matrices containing the geometric isomers fumarate diNa and maleate diNa are compared in Figure 4.3. Dissolution test kinetic parameters, extracted from Table 4.5, are shown in Table 4.7.

Both salts markedly accelerated drug release from HPMC matrices in comparison with the control tablet (Section 4.5.2) and this behaviour can be described through their water affinity, which is higher than HPMC. Fumarate and maleate both act as kosmotropic salts in the Hofmeister series, altering the solubility of HPMC by competing for and removing water from the polymer hydration sheath. In the hydrating matrix tablet this leads to suppression of polymer swelling and gel layer formation.

The release rate constant (k) and the time to 80% cumulative drug release ($T_{80\%}$) (Table 4.7) showed drug release from HPMC matrices containing fumarate (trans form) was significantly more quickly than those containing maleate (cis form) ($p < 0.05$, one-way ANOVA; $f_1 = 28.66$, $f_2 = 33.25$). This corresponds with results from the study of these salts on HPMC solutions which suggested fumarate exhibited a stronger potential to promote the molecular aggregation of HPMC (or perhaps be involved in molecular cross-linking through stronger intermolecular bonds) than maleate which indicated it had only a weak interaction with the polymer (Chapter 3). These molecular differences would influence polymer solvation and therefore the trans form would have more ability than the cis form to destroy the controlled release properties of HPMC matrix tablets.

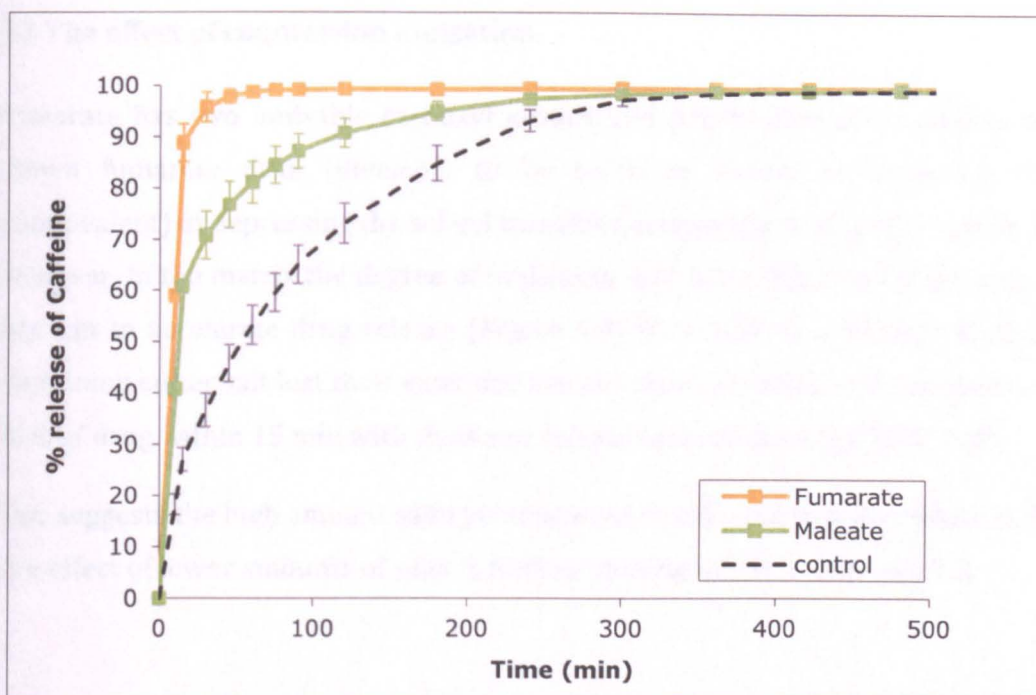


Figure 4.3 The effect of fumarate/maleate geometric isomerism on the drug release profile of HPMC matrices. 8mm, 250mg matrices containing 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. USP I , 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

Organic salts	T _{50%}	T _{80%}	Modified power law (Ford et al 1987)			Linear regression	
			k	n	r ²	k	r
<i>Control</i>							
No salt (dextrose used as a diluent)	66	178	9.58	0.419	0.9992	1.32	0.9963
<i>Geometric isomerism</i>							
Fumarate diNa	9	14	90.33 ^(a)	0.022 ^(a)	0.9492 ^(a)	5.91	1.0000
Maleate diNa	12	56	54.25 ^(c)	0.106 ^(c)	0.9742 ^(c)	4.06	1.0000

Table 4.7 The effect of fumarate/maleate geometric isomerism of the organic salts on drug release kinetics using the modified power law and linear regression. Modified power law is fitted up to 80% cumulative release, but the fast release matrices were calculated up to 99% cumulative release. Linear regression is fitted for the early release. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. $T_{50\%}$ and $T_{80\%}$ are the time to 50% and 80% cumulative drug release respectively. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient. (a) Drug release >80% within 15 min. (b) Drug release >80% within 1h.

(b) The effect of counter-ion ionisation

Fumarate has two ionisable carboxyl groups and previous solution studies had shown fumarate diNa (divalent) to be twice as potent as fumarate NaH (monovalent) in depressing the sol:gel transition temperature (SGTT) (Chapter 3). However, in the matrix the degree of ionisation, had little effect on the potency of this salt to accelerate drug release (Figure 4.4) ($f_1 = 1.37$, $f_2 = 92.08$). Matrices containing either salt lost their extended release characteristics, and released over 80% of drug within 15 min with the same release rate constant (k)(Table 4.8).

This suggests the high amount salts present was too extreme to differentiate them. The effect of lower amounts of salts is further investigated in section 4.5.3.3.

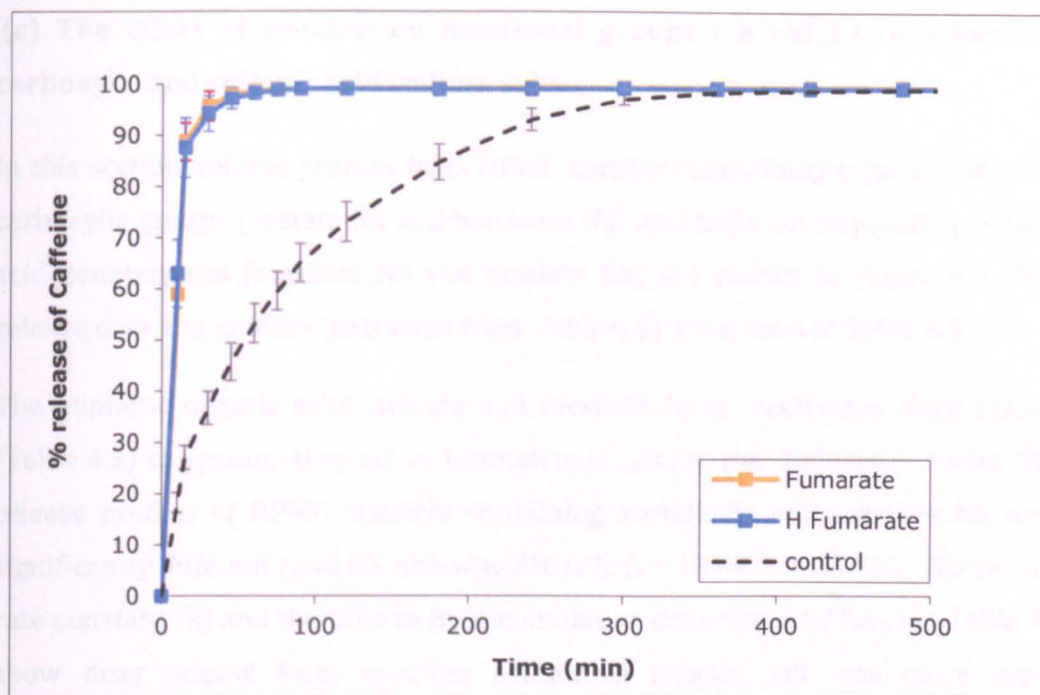


Figure 4.4 The effect of ionisation of fumarate salts on the drug release profile of HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

Organic salts	T _{50%}	T _{80%}	Modified power law (Ford et al 1987)			Linear regression	
			k	n	r ²	k	r
<u>Control</u>							
No salt (dextrose used as a diluent)	66	178	9.58	0.419	0.9992	1.32	0.9963
<u>Ionization</u>							
Fumarate Na H	8	14	86.91(a)	0.032(a)	0.9585(a)	5.91	0.9983
Fumarate diNa	9	14	90.33(a)	0.022(a)	0.9492(a)	5.91	1.0000

Table 4.8 The effect of ionisation of fumarate salts on drug release kinetics using the modified power law and linear regression. Modified power law is fitted up to 80% cumulative release, but the fast release matrices were calculated up to 99% cumulative release. Linear regression is fitted for the early release. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. $T_{50\%}$ and $T_{80\%}$ are the time to 50% and 80% cumulative drug release respectively. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient.

(a) Drug release >80% within 15 min.

(c) The effect of counter-ion functional groups : a comparison between carboxylic and sulfonic acid sodium salts

In this section, release profiles from HPMC matrices containing organic salts with carboxylic groups (acetate Na and benzoate Na) and their corresponding sulfonic acid counterparts (mesilate Na and besilate Na) are shown in Figure 4.6. The release data and kinetics (extracted from Table 4.5) are shown in Table 4.9.

The aliphatic organic salts, acetate and mesilate both accelerated drug release (Table 4.5) suggesting they act as kosmotropic salts in the Hofmeister series. The release profiles of HPMC matrices containing acetate Na and mesilate Na were significantly different ($p < 0.05$, one-way ANOVA; $f_1 = 15.64$, $f_2 = 33.77$). The release rate constant (k) and the time to 80% cumulative drug release ($T_{80\%}$) in Table 4.9 show drug release from matrices containing acetate salt was more rapid. Surprisingly, however, no difference was detected in their effect on the SGTT of HPMC solutions (Chapter 3). This suggests another mechanism may be responsible for differences, perhaps differences in osmotic transport into the matrix core.

In contrast however, the aromatic organic salts, benzoate and besilate both retarded drug release, and besilate matrices were significantly slower than benzoate ($p < 0.05$, one-way ANOVA; $f_1 = 19.06$, $f_2 = 49.26$). This corresponds to their ability to raise SGTT of HPMC solutions which assumed to prolong drug release from HPMC matrices by solubilising HPMC (Chapter 3). Pygall et al (2011) have provided evidence that a benzoic acid derivative, sodium meclofenamate, a self associating drug, exhibits drug:HPMC association which can be detected rheologically, and by small-angle neutron scattering. Benzoate and besilate might solubilise HPMC through a similar mechanism, forming π -stacking aggregates around the hydrophobic domain of HPMC. Besilate, with a sulphur atom within its structure may be able to form the self-assembled structure better than benzoate through intermolecular π - π and sulphur-sulphur interactions (Van der Waals) between adjacent molecules (Sasaki et al 2006; Hao et al 2012) as shown in Figure 4.5. The stacking of these polar molecules around the hydrophobic domains of HPMC will make these areas of the polymer chain more attractive to water and

stabilise the hydration sheath. The consequences of this could be more rapid hydration, swelling and gel layer formation in the matrix tablet.

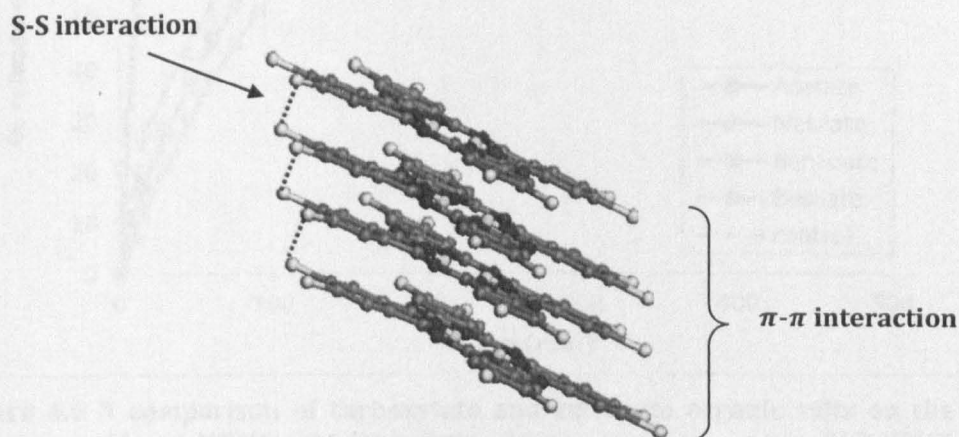


Figure 4.5 The intermolecular π - π and sulphur-sulphur (S-S) interactions between adjacent molecules of a stacking aromatic species such as besilate (Taken from Hao et al 2011).

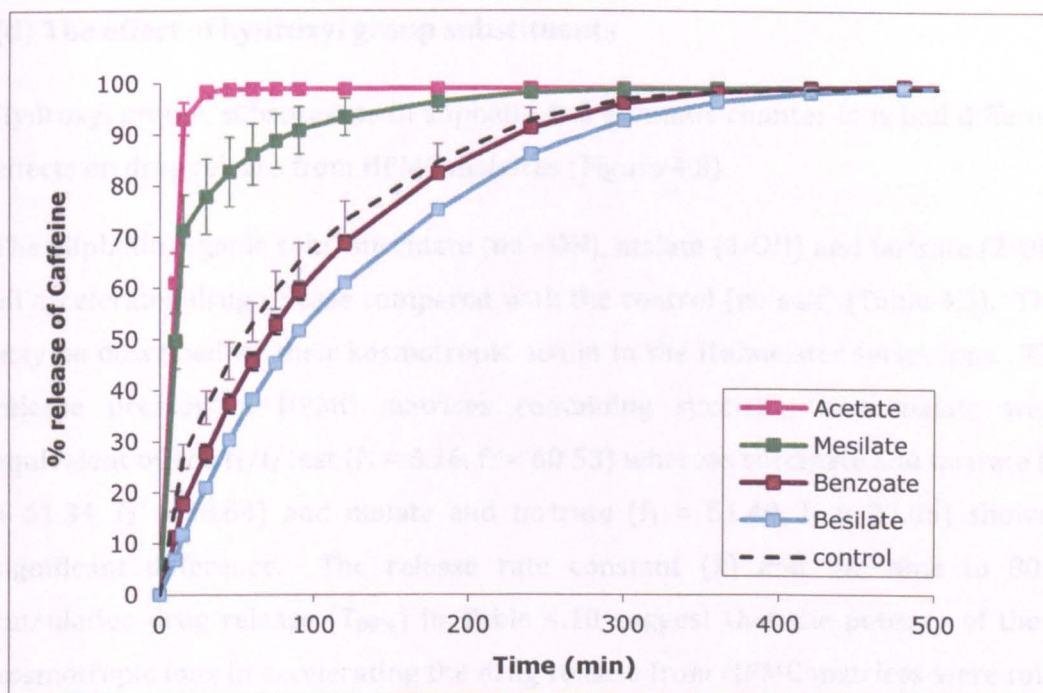


Figure 4.6 A comparison of carboxylate and sulfonate organic salts on the drug release profile of HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

Organic salts	T _{50%}	T _{80%}	Modified power law (Ford et al 1987)			Linear regression	
			k	n	r ²	k	r
<u>Control</u>							
No salt (dextrose used as a diluent)	66	178	9.58	0.419	0.9992	1.32	0.9963
<u>Functional groups</u>							
Acetate Na	8	13	96.84(a)	0.005(a)	0.9378(a)	6.19	0.9999
Mesilate Na	10	37	61.57(c)	0.088(c)	0.9940(c)	4.78	0.9994
Benzoate Na	69	170	7.56	0.475	0.9989	1.18	0.9992
Besilate Na	86	206	4.87	0.542	0.9985	0.67	0.9982

Table 4.9 A comparison of carboxylate and sulfonate organic salts on drug release kinetics using the modified power law and linear regression. Modified power law is fitted up to 80% cumulative release, but the fast release matrices were calculated up to 99% cumulative release. Linear regression is fitted for the early release. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. $T_{50\%}$ and $T_{80\%}$ are the time to 50% and 80% cumulative drug release respectively. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient.

(a) Drug release >80% within 15 min. (b) Drug release >80% within 1h.

(d) The effect of hydroxyl group substituents

Hydroxyl groups substituents in aliphatic and aromatic counter ions had different effects on drug release from HPMC matrices (Figure 4.8).

The aliphatic organic salts, succinate (no -OH), malate (1-OH) and tartrate (2-OH) all accelerated drug release compared with the control (no salt) (Table 4.5). This may be described by their kosmotropic action in the Hofmeister series ions. The release profiles of HPMC matrices containing succinate and malate were equivalent by the f_1/f_2 test ($f_1 = 6.16$, $f_2 = 60.53$) whereas succinate and tartrate ($f_1 = 61.34$, $f_2 = 23.84$) and malate and tartrate ($f_1 = 51.40$, $f_2 = 27.05$) showed significant difference. The release rate constant (k) and the time to 80% cumulative drug release ($T_{80\%}$) in Table 4.10 suggest that the potency of these kosmotropic ions in accelerating the drug release from HPMC matrices were rank ordered as follows:

$$\text{Succinate (no -OH)} \geq \text{Malate (1-OH)} > \text{Tartrate (2-OH)}$$

This rank order is reversed with respect to the effect of these salts on HPMC solutions (Chapter 3) in which we postulated that the increasing numbers of hydroxyl groups, provide more potential for interaction with the hydrogen bonded structure of water, and would enhance the effects of the parent molecule in dehydrating the polymer hydration sheath.

A reason why tartrate exhibited the lowest potential to accelerate drug release may be because of the difference in molecular orientation in solution and as a solid. In the solution studies, HPMC and tartrate were separately hydrated before mixing. In this case, the orientation of tartrate is a hydrated free anion (Figure 4.7a) which has higher affinity to water than succinate and malate. In contrast, in the solid state, the orientation of tartrate is more rigid because of the intramolecular bond between carboxylate and alcoholic hydroxyl groups of the ligand (Rodrigues et al 2009). In this case, energy is needed to break this crystalline structure before salt hydration can occur, leading to slower dissolution and less ability to compete for available water with HPMC (Figure 4.7b)

In the case of aromatic salts, both benzoate (no -OH) and salicylate (1-OH) retarded drug release (Table 4.5), but benzoate was significantly slower ($p < 0.05$, one-way ANOVA; $f_1 = 15.94$, $f_2 = 43.23$). This was the opposite rank order to their solution behaviour, in which salicylate was more potent in elevating SGTT. This might be because salicylate with its -OH, although able to form stacking structure, also interacts with the hydrogen bonded structure of water and therefore better compete for polymer water of hydration. This would lead to slower gel layer formation. Benzoate however is able to solubilise HPMC by better molecular stacking, and without the extra competing effects.

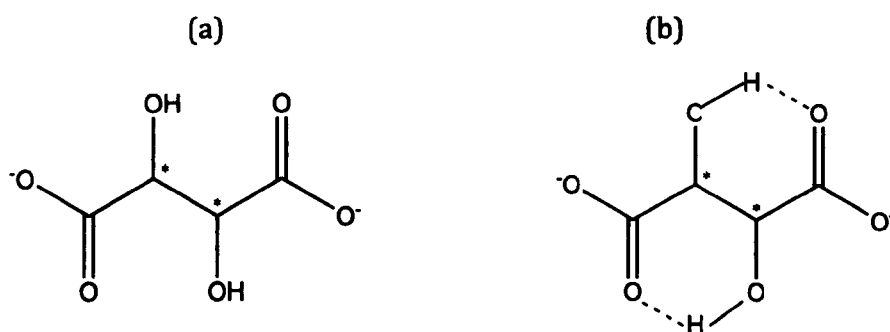


Figure 4.7 The orientation of tartrate structure in (a) solution (b) solid.

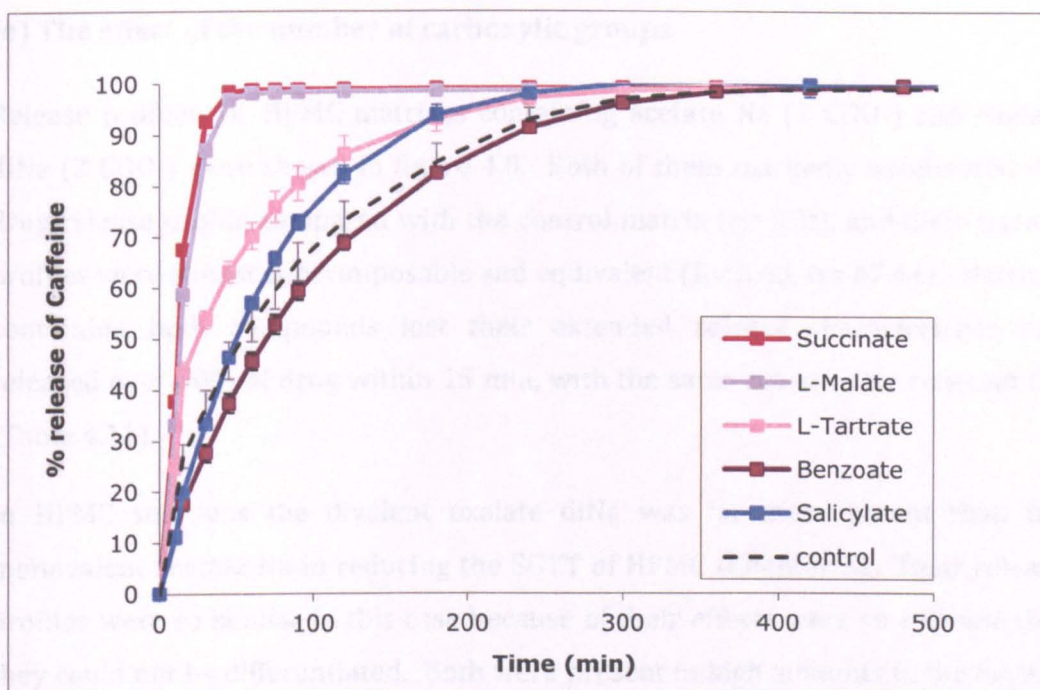


Figure 4.8 The effect of hydroxyl group substituents on the release profile of HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

Organic salts	T _{50%}	T _{80%}	Modified power law (Ford et al 1987)			Linear regression	
			k	n	r ²	k	r
<u>Control</u>							
No salt (dextrose used as a diluent)	66	178	9.58	0.419	0.9992	1.32	0.9963
<u>The presence of hydroxyl group(s)</u>							
Succinate diNa	12	23	78.79 ^(b)	0.062 ^(b)	0.9034 ^(b)	4.40	0.9926
Malate diNa	13	27	64.46 ^(b)	0.114 ^(b)	0.9292 ^(b)	3.83	0.9930
Tartrate diNa	25	89	27.13	0.251	0.9985	2.84	0.9954
Benzoate Na	69	170	7.56	0.475	0.9989	1.18	0.9992
Salicylate Na	50	113	9.36	0.472	0.9977	0.95	0.9935

Table 4.10 The effect of the presence of hydroxyl group(s) within the organic salts on drug release kinetics using the modified power law and linear regression. Modified power law is fitted up to 80% cumulative release, but the fast release matrices were calculated up to 99% cumulative release. Linear regression is fitted for the early release. 8mm, 250mg matrices contain 30%HPMC E4M, 10% caffeine anhydrous, 60% organic salt. $T_{50\%}$ and $T_{80\%}$ are the time to 50% and 80% cumulative drug release respectively. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient.
(a) Drug release >80% within 30 min.

(e) The effect of the number of carboxylic groups

Release profiles for HPMC matrices containing acetate Na (1 COO-) and oxalate diNa (2 COO-) were shown in figure 4.8. Both of them markedly accelerated the drug release profile compared with the control matrix (no salt), and their release profiles were almost superimposable and equivalent ($f_1 = 5.43$, $f_2 = 67.44$). Matrices containing both compounds lost their extended release characteristics and released over 80% of drug within 15 min, with the same release rate constant (k) (Table 4.11).

In HPMC solutions the divalent oxalate diNa was far more potent than the monovalent acetate Na in reducing the SGTT of HPMC (Chapter 3). Their release profiles were so similar in this case because of their effects were so extreme that they could not be differentiated. Both were present in high amounts in the matrix. The effect of lower salt contents was investigated and will be discussed in section 4.5.3.3.

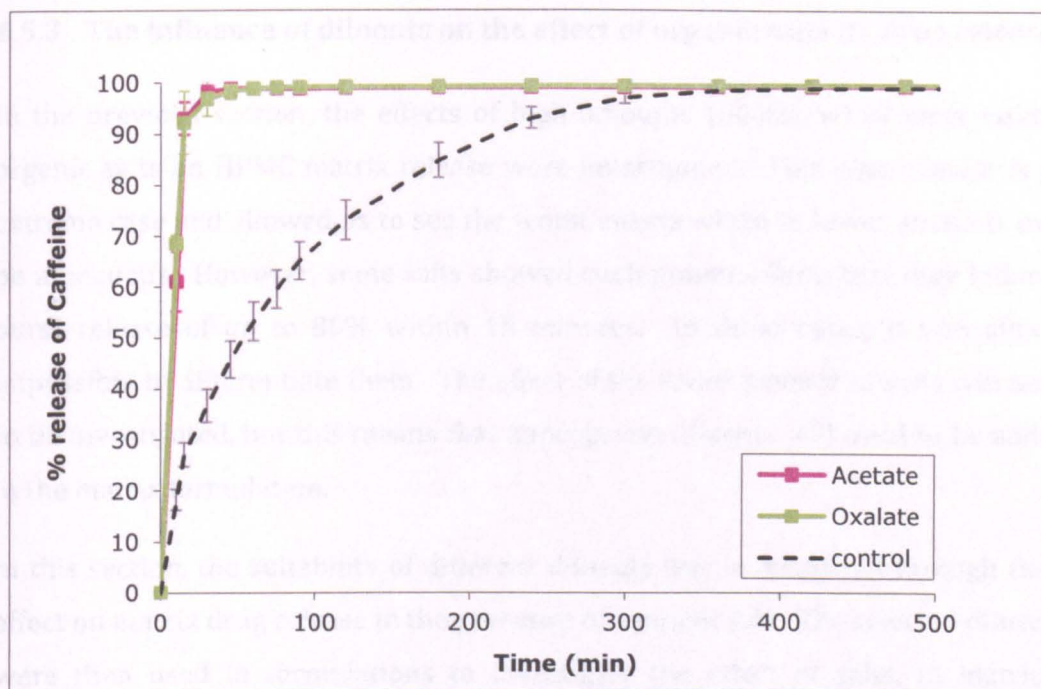


Figure 4.9 The effect of the number of carboxyl groups on the release profile of HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

Organic salts	T _{50%}	T _{80%}	Modified power law (Ford et al 1987)			Linear regression	
			k	n	r ²	k	r
<i>Control</i>							
No salt (dextrose used as a diluent)	66	178	9.58	0.419	0.9992	1.32	0.9963
<i>The number of carboxylic groups</i>							
Acetate Na	8	13	96.84 ^(a)	0.005 ^(a)	0.9378 ^(a)	6.19	0.9999
Oxalate diNa	7	12	92.77 ^(a)	0.017 ^(a)	0.9630 ^(a)	6.25	0.9930

Table 4.11 The effect of the number of carboxyl groups on drug release kinetics using the modified power law and linear regression. Modified power law is fitted up to 80% cumulative release, but the fast release matrices were calculated up to 99% cumulative release. Linear regression is fitted for the early release. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% organic salt. $T_{50\%}$ and $T_{80\%}$ are the time to 50% and 80% cumulative drug release respectively. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient. (a) Drug release >80% within 15 min.

4.5.3 The influence of diluents on the effect of organic salts on drug release

In the previous section, the effects of high amounts (60%w/w) of incorporated organic salts on HPMC matrix release were investigated. This high content is an extreme case and allowed us to see the worst effects which in lower amounts may be innocuous. However, some salts showed such potent effects that they induced burst release of up to 80% within 15 minutes. In these cases, it was almost impossible to differentiate them. The effect of the lower amount of salts will need to be investigated, but this means that appropriate diluents will need to be added in the matrix formulation.

In this section, the suitability of different diluents was investigated through their effect on matrix drug release in the presence of a potent salt. The selected diluents were then used in formulations to investigate the effect of salts, in matrices containing a low salt content (10%w/w).

4.5.3.1 The effect of diluents on drug release from HPMC matrices

Dextrose (as a fully soluble diluent), microcrystalline cellulose (MCC, an insoluble diluent), or partially pregelatinised starch (Starch 1500®, as an intermediate solubility diluent) were investigated alone or in combination, to find the most suitable diluents for this study. The composition of these matrices is shown in Table 4.2.

Compression pressure – hardness profiles of HPMC matrix tablets containing these are shown in Figure 4.10 and drug release data and kinetics in Table 4.12.

The effect of these diluents on the release profiles of the matrices were also investigated with different types of HPMC, (HPMC E4M, HPMC E4M (63-90µm fraction) and HPMC K4M). Matrices containing fractionated HPMC E4M with MCC and its mixture with dextrose were exceptional as their exponent (n) was <0.4 and they showed the potential for burst release. The diffusional exponent (n) of all other formulations was ~ 0.5 suggesting a normal diffusion-controlled release mechanism. The effect of each diluent on the HPMC matrix is discussed separately :

Partially pregelatinised starch (Starch 1500):

Figure 4.11 shows the effect of partially pregelatinised starch on the drug release profiles of HPMC matrices. Partially pregelatinised starch caused a markedly lower release rate (k) compared with the other diluents (Table 4.12, Formulation D). All matrices containing partially pregelatinised starch showed good extended release characteristics and release profiles were statistically equivalent ($f_1 = 4.47$, $f_2 = 75.50$ for E4M and K4M; $f_1 = 2.96$, $f_2 = 80.62$ for E4M and fractionated E4M). Faster profiles were obtained by adding dextrose 50:50. The release profiles of matrices containing these mixtures (Formulation E) were equivalent ($f_1 = 7.51$, $f_2 = 61.09$ for E4M and K4M; $f_1 = 11.33$, $f_2 = 52.58$ for E4M and fractionated E4M). The lack of differences between different formulations might be because of the synergistic effects between partially pregelatinised starch and HPMC. Both polymers hydrate, swell, and contribute to the gel layer barrier leading overall to a more concentrated gel and therefore more delayed water penetration (Michailova et al 2001; Levina & Rajabi-Siahboomi 2004). Although the matrices containing partially pregelatinised starch exhibited the longest extended release compared with dextrose and MCC, tablet hardness values were low (Figure 4.10).

Microcrystalline cellulose (MCC):

Figure 4.12 shows the effect of MCC on the drug release profiles. MCC exhibited widely different effects between HPMC types from delayed release (for K4M) to fast release (for fractionated E4M). Release profiles for all matrices containing MCC (Formulation F) were significantly different ($p < 0.05$, one-way ANOVA; $f_1 = 33.34$, $f_2 = 24.45$ for E4M and K4M; $f_1 = 53.19$, $f_2 = 13.22$ for E4M and fractionated E4M). The mixture of MCC and dextrose (Formulation G) lessened this effect but their release profiles were still different ($f_1 = 26.42$, $f_2 = 25.45$ for E4M and K4M; $f_1 = 20.67$, $f_2 = 38.67$ for E4M and fractionated E4M). Table 4.12 shows the rank order of the release rate constant (k) and the time to 80% cumulative drug release ($T_{80\%}$) were as follows:

Fractionated E4M > E4M > K4M

← Release rate →

Fractionated E4M < E4M < K4M

————— $T_{80\%}$ —————→

This rank order corresponds to the likely hydration of the polymer in which HPMC K4M is the most rapidly hydrated. The argument is that faster hydrating derivatives will form gels more quickly and prevent rapid initial dissolution of surface particles (Doelker 1987), however this has been disputed (Li et al 2005). In this case, the most hydrophilic grade is HPMC K4M. Fractionated HPMC E4M (63-90 μ m) in which the hydration rate is even slower than E4M (which containing particle sizes < 63 μ m) exhibited the burst release of the tablet. This might because of the ability of MCC to alter the water penetration into the matrix system. Levina & Rajabi-Siahboomi (2004) found that matrices containing MCC rapidly absorbed water into the tablets which these quick water uptake and water front movement into the matrix tablet can lead to a higher release rate.

MCC, has some advantages : tablets were harder than with dextrose and partially pregelatinised starch (Figure 4.10) but the high variability of release profiles with respect to HPMC substitution and particle size differences, is a worrying disadvantage.

Dextrose:

Figure 4.13 shows the effect of Dextrose on drug release profiles of HPMC matrices. Release profiles for HPMC matrices of E4M and K4M were slightly different ($f_1 = 14.17$, $f_2 = 43.52$) whereas those of E4M and fractionated E4M were similar ($f_1 = 8.24$, $f_2 = 54.51$). The profiles were much less variable than MCC. The release rate constant (k) and the time to 80% cumulative drug release ($T_{80\%}$) suggest a rate midway between partially pregelatinised starch and MCC (Table 4.12, Formulation C). Dextrose is a soluble diluent which may act as a pore former to make the gel structure more porous and weaker, leading to an increased drug release rate (Li 2005, Yang & Fassihi 1997). With dextrose, matrix tablets were harder than those with partially pregelatinised starch but softer than those with MCC, and the drug release rate was not unduly sensitive to HPMC type.

Formulation	HPMC E4M				HPMC E4M fractionated				HPMC K4M			
	T _{80%}	k	n	r ²	T _{80%}	k	n	r ²	T _{80%}	k	n	r ²
C (dextrose)	206	6.65	0.477	0.9982	178	9.58	0.419	0.9992	265	3.88	0.552	0.9973
D (partially pregelatinised starch)	465	4.16	0.487	0.9976	470	3.83	0.497	0.9994	480	3.38	0.520	0.9996
E (Dextrose+ partially pregelatinised starch)	313	4.74	0.498	0.9982	270	7.26	0.434	0.9994	331	2.93	0.581	0.9953
F (MCC)	230	11.61	0.366	0.9989	40	30.33	0.305	1.0000	434	3.42	0.523	0.9990
G (Dextrose+ MCC)	134	12.24	0.401	0.9985	90	23.63	0.281	0.9996	278	4.88	0.504	0.9986

Table 4.12 The effect of diluents on drug release kinetics using the modified power law. Fitted up to 80% cumulative release. Modified power law is described by Ford et al (1987). The detail of formulation C, D, E, F and G is in section 4.4.3 table 4.2. T_{80%} is the time to 80% drug release. k is the kinetic constant. n is the diffusional exponent. r² is coefficient of determination.

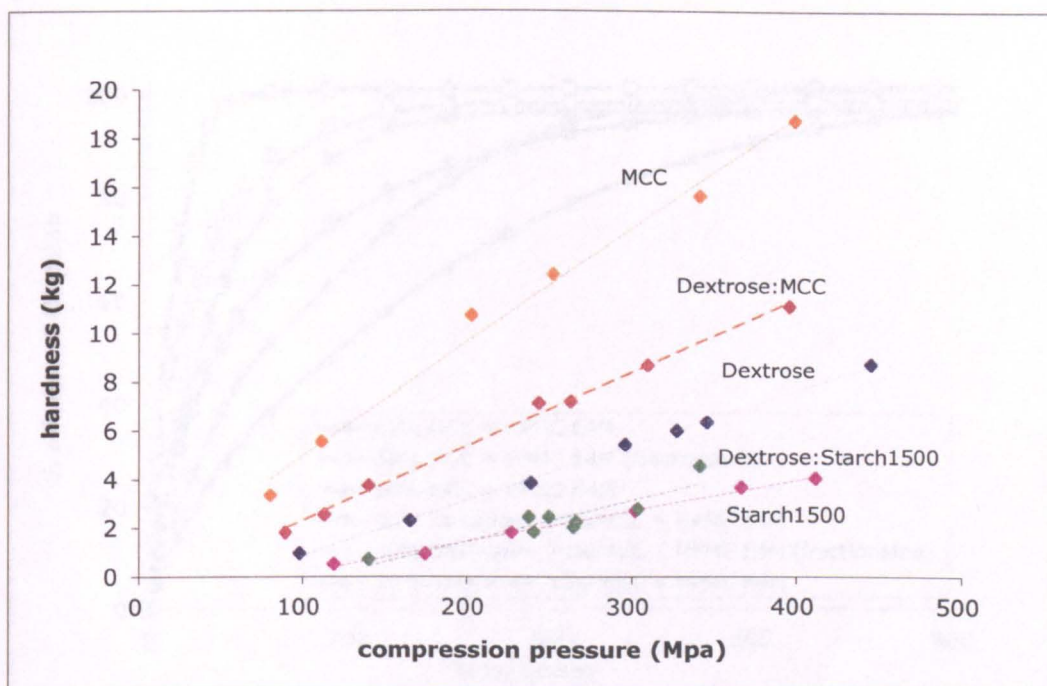


Figure 4.10 Compression pressure – hardness profile for HPMC matrix tablets containing different diluents. 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, qs diluents.

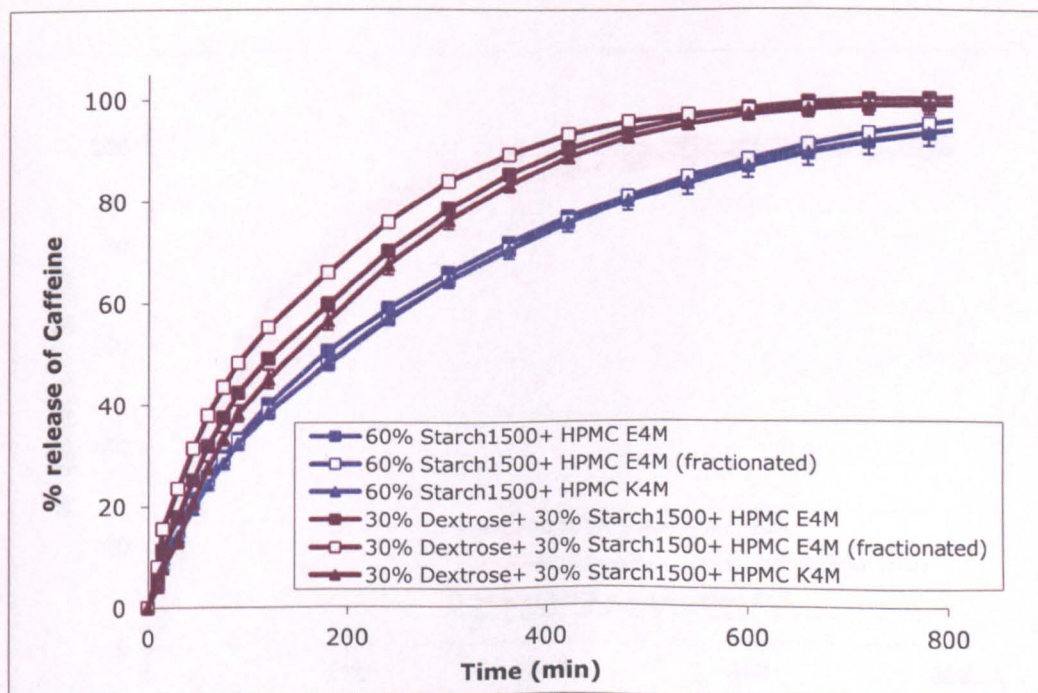


Figure 4.11 The effect of partially pregelatinised starch (Starch1500) on the dissolution profile of HPMC matrices (E4M, E4M (63-90µm fraction), and K4M). 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, qs diluents. USP I, 100rpm, 37°C in water. Mean (n=3) ± 1S.D.

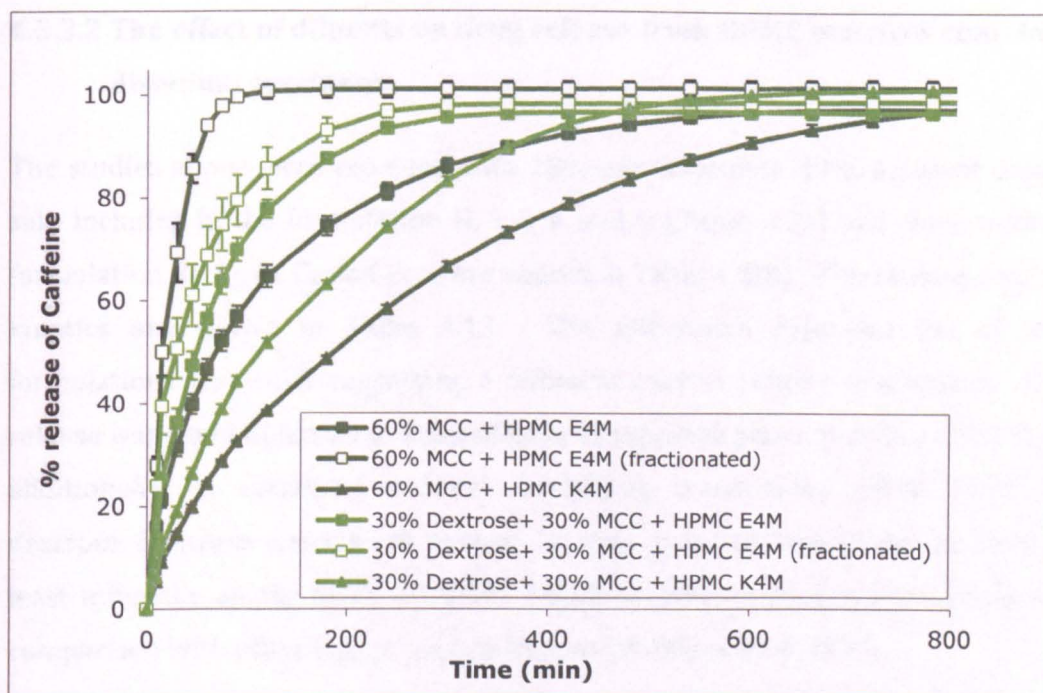


Figure 4.12 The effect of MCC on the dissolution profile of HPMC matrices (E4M, E4M (63-90 μ m fraction), and K4M). 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, qs diluents. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D.

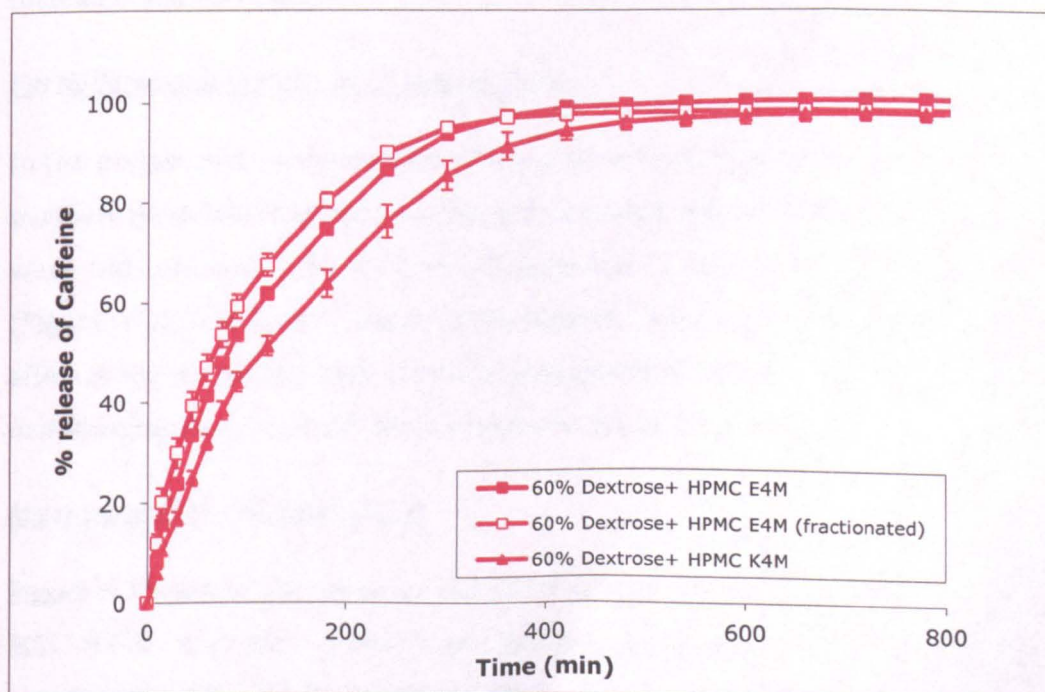


Figure 4.13 The effect of Dextrose on the dissolution profile of HPMC matrices (E4M, E4M (63-90 μ m fraction), and K4M). 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, qs diluents. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D.

4.5.3.2 The effect of diluents on drug release from HPMC matrices containing disodium succinate

The studies above were repeated with 10%w/w succinate diNa, a potent organic salt, included in the formulation H, I, J, K and L (Table 4.3a) and their controls, formulation C_H, C_I, C_J, C_K and C_L, were shown in Table 4.3(b). The release data and kinetics are shown in Table 4.13. The diffusional exponent (n) of most formulations was ~0.5 suggesting a diffusion-control release mechanism. Drug release was rapid in the same formulations as reported above (Section 4.5.3.1) and additionally, in succinate matrices containing fractionated HPMC E4M and dextrose. Dextrose was chosen in these studies as it has been shown to have the least influence on the SGTT of HPMC solutions, and on drug release profiles in comparison with other sugars such as lactose (Williams et al 2009).

The effect of the each diluent in the presence of succinate diNa is discussed separately, and the graphs show a comparison between matrices containing 10%w/w succinate diNa, and control formulations containing 10% dextrose instead of the succinate.

Partially pregelatinised starch (Starch 1500):

In the presence of succinate diNa (Formulation I and J), matrices with a diluent of partially pregelatinised starch exhibited extended release and the release profiles were not different from control (Formulation C_I and C_J) in all types of HPMC (Figure 4.14; f₁ & f₂ were shown in the figure). This suggests that the synergistic effect between HPMC and partially pregelatinised starch was still effective in maintaining the controlled release performance of these matrices

Microcrystalline cellulose (MCC):

Figure 4.15 shows the effect of succinate diNa on the drug release profiles of MCC HPMC matrices. Release profiles for succinate-containing matrices were significantly different from control (f₁ & f₂ values are shown in the figure) and release rates were widely different among HPMC types, and were either higher or lower than the controls. A mixture of MCC and dextrose (Formulation L) lessened

the difference between matrices with and without succinate. Replacing MCC by dextrose or succinate diNa replaces 10% MCC with a more soluble diluents which may also osmotically attract water into the system, leading to more rapid hydration of HPMC. This may be the reason why the release rate of matrices with succinate diNa was slower than the control for HPMC E4M. On the other hand, the release rate of HPMC K4M matrices with succinate diNa was higher than control. This might because succinate diNa competed for the available water, leading to the slower gel formation than control.

Dextrose:

Figure 4.16 shows the effect of succinate diNa on drug release profiles of HPMC matrices containing dextrose as a diluent. In the presence of succinate diNa, the release profiles for E4M and K4M matrix were equivalent to control whereas those for fractionated E4M were significantly higher than control (f_1 & f_2 values are shown in the figure). Matrices of fractionated HPMC E4M, succinate diNa appear to be more sensitive than others (see previous section) and succinate diNa which is kosmotropic salt in a Hofmeister series, was perhaps potent enough to compete for the available water suppress polymer hydration and gel layer formation. The more tolerant polymer grades E4M and K4M produced gel layers and extended release.

Figure 4.17 and 4.18 replots the previous graphs to compare the different diluents and polymer grades directly, both with and without the succinate salt. Without salt, there was no difference between matrices of HPMC E4M and fractionated E4M when using dextrose or partially pregelatinised starch as a diluent. Using an MCC diluent matrices were different, as discussed in section 4.5.3.1. With succinate salt, the differences were seen using dextrose ($f_1=97.45$, $f_2=6.11$), MCC ($f_1=18.81$, $f_2=42.71$) and partially pregelatinised starch ($f_1=23.21$, $f_2=38.40$). Dextrose was the most sensitive diluent.

In conclusion, partially pregelatinised starch appeared to mask the differences of HPMC particle size and substitution and 10% of this organic salt. This may be

advantageous to a formulator, but is a disadvantage in this study, as it may not allow us to differentiate the effects of different organic salts. MCC is also not appropriate, as its influence on HPMC matrices is highly variable. Moreover, this insoluble diluent may have a direct influence on HPMC gel formation by itself and so the obtained results might be the combination of both MCC and salts. Dextrose appears to be the most suitable diluent to be used in this study because it exhibited small differences among HPMC types, but the effect of salt can be differentiated from the control. These all results suggest that using dextrose with fractionated HPMC E4M is the most suitable to differentiate the effects of organic salts used in this study.

Note: Although Ford et al (1985a, b) stated that the compression pressure rarely influences drug release from HPMC matrices, Levina & Rajabi-Siahboomi (2004) found that the applied compression force affected drug release rate depended on the type of diluent. In this study, the effect of compression force on drug release from HPMC using dextrose as a diluent was investigated. The results are shown in Appendix 4 and suggested that the different compression force do not influence drug release. The compression pressure at 160MPa was used in the study of the effect of organic salts on HPMC matrices because it was within the linear range of compression pressure-hardness profile for all organic salts used in this study (data not be shown).

Formulation	HPMC E4M				HPMC E4M fractionated				HPMC K4M			
	T _{80%}	k	n	r ²	T _{80%}	K	n	r ²	T _{80%}	k	n	r ²
H (dextrose)	225	5.91	0.487	0.9993	18	68.16	0.083	0.9982	251	3.30	0.588	0.9991
I (partially pregelatinised starch)	385	4.38	0.493	0.9995	476	1.34	0.675	0.9593	440	2.81	0.555	0.9982
J (Dextrose+ partially pregelatinised starch)	285	4.47	0.518	0.9988	259	6.66	0.453	0.9998	315	3.40	0.559	0.9979
K (MCC)	160	11.53	0.396	0.9988	115	19.83	0.304	0.9989	316	4.41	0.508	0.9986
L (Dextrose+ MCC)	233	5.37	0.505	0.9982	60	40.08	0.182	0.9993	267	3.35	0.578	0.9976

Table 4.13 The effect of diluents on drug release kinetics of HPMC matrices containing disodium succinate using the modified power law. Fitted up to 80% cumulative release. Modified power law is described by Ford et al (1987). The detail of formulation H, I, J, K and L and their controls is in section 4.4.3 table 4.3. T_{80%} is the time to 80% drug release. k is the kinetic constant. n is the diffusional exponent. r² is coefficient of determination.

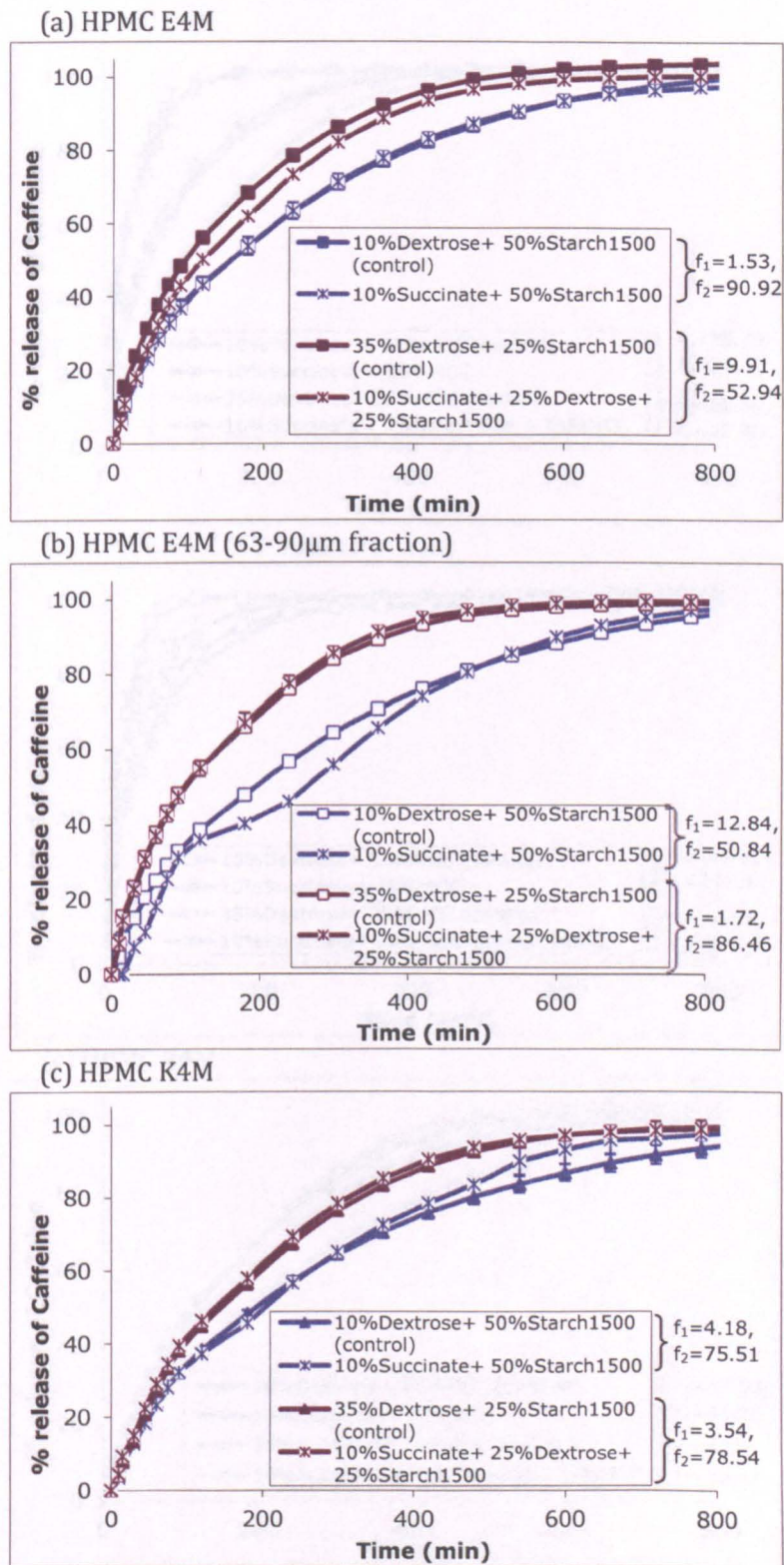


Figure 4.14 The effect of partially pregelatinised starch (Starch1500) on the dissolution profile of HPMC matrices containing disodium succinate which (a) E4M (b) E4M (63-90 μ m fraction) and (c) K4M. 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, 10% succinate diNa qs diluents. The detail of these formulations is section 4.4.3 table 4.3. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D.

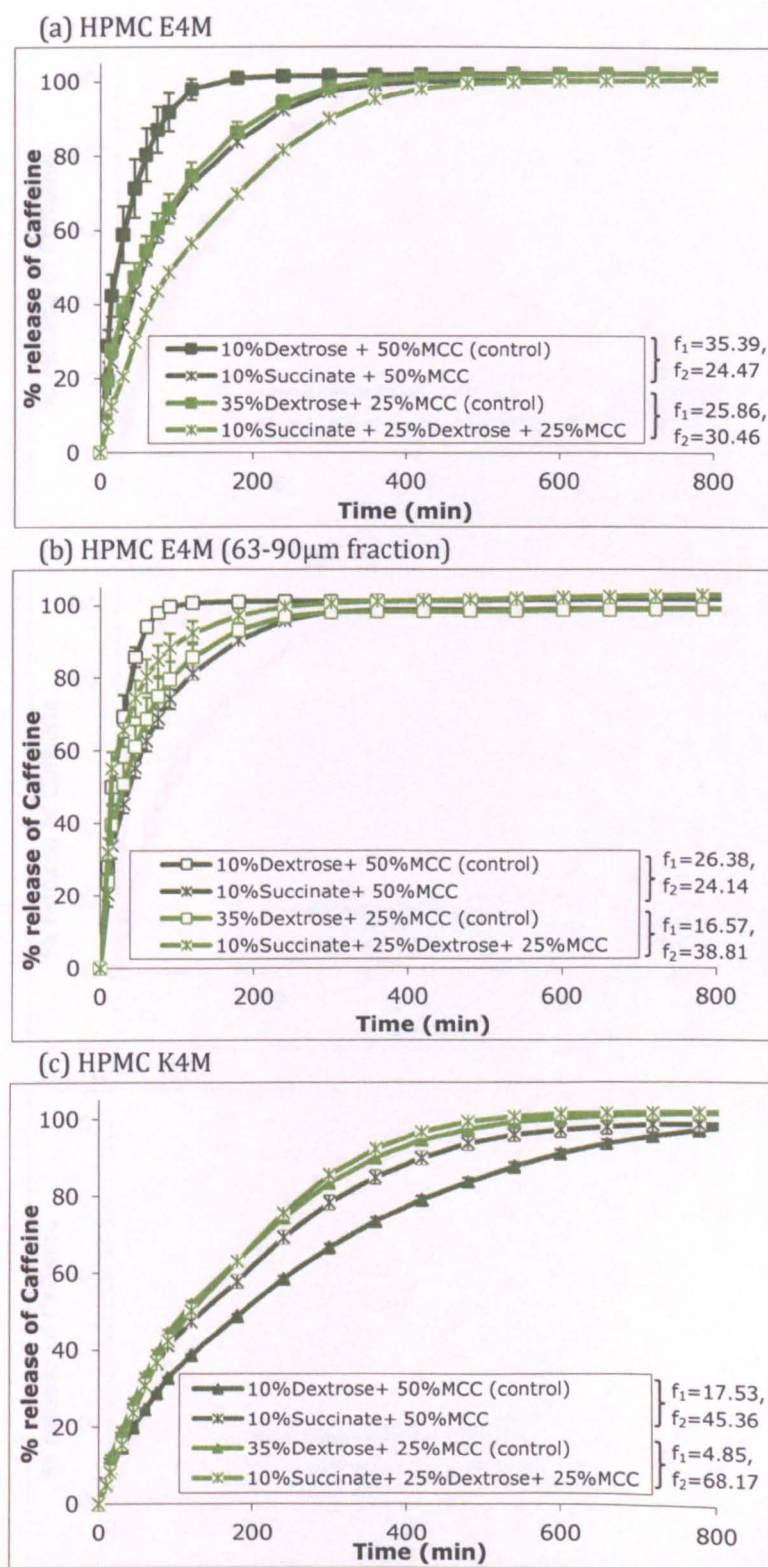
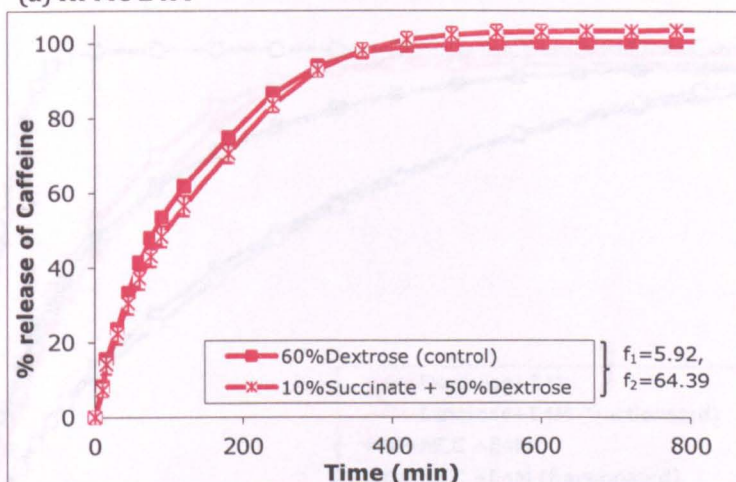
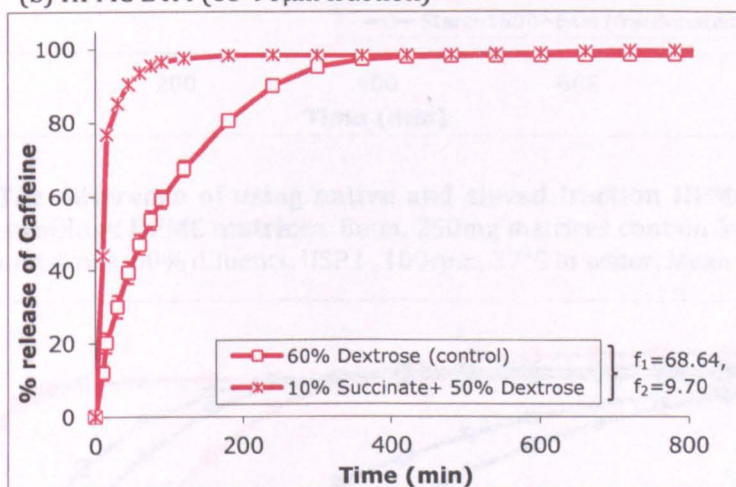


Figure 4.15 The effect of MCC on the dissolution profile of HPMC matrices containing disodium succinate which (a) E4M (b) E4M (63-90 μ m fraction) and (c) K4M. 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, 10% succinate diNa qs diluents. The detail of these formulations is section 4.4.3 table 4.3. USP I , 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

(a) HPMC E4M

(b) HPMC E4M (63-90 μ m fraction)

(c) HPMC K4M

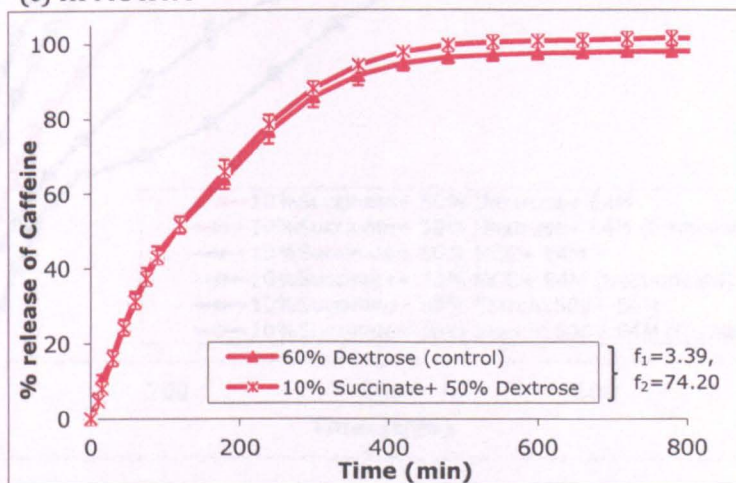


Figure 4.16 The effect of Dextrose on the dissolution profile of HPMC matrices containing disodium succinate which (a) E4M (b) E4M (63-90 μ m fraction) and (c) K4M. 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, 10% succinate diNa qs diluents. The detail of these formulations is section 4.4.3 table 4.3. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D.

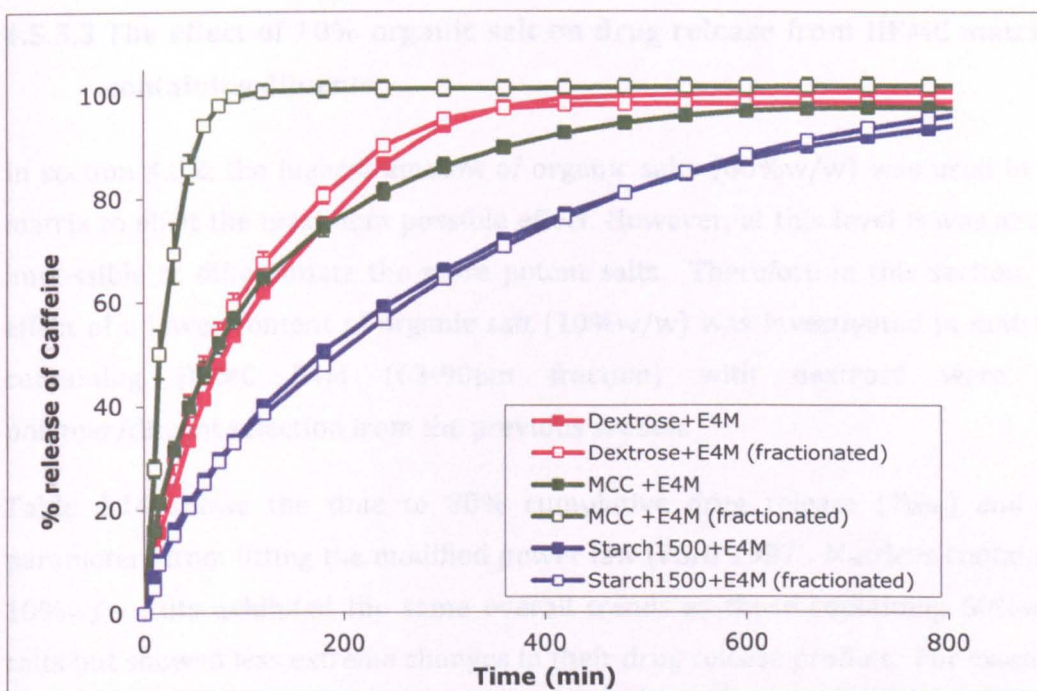


Figure 4.17 The difference of using native and sieved fraction HPMC E4M on the drug release profile of HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 60% diluents. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

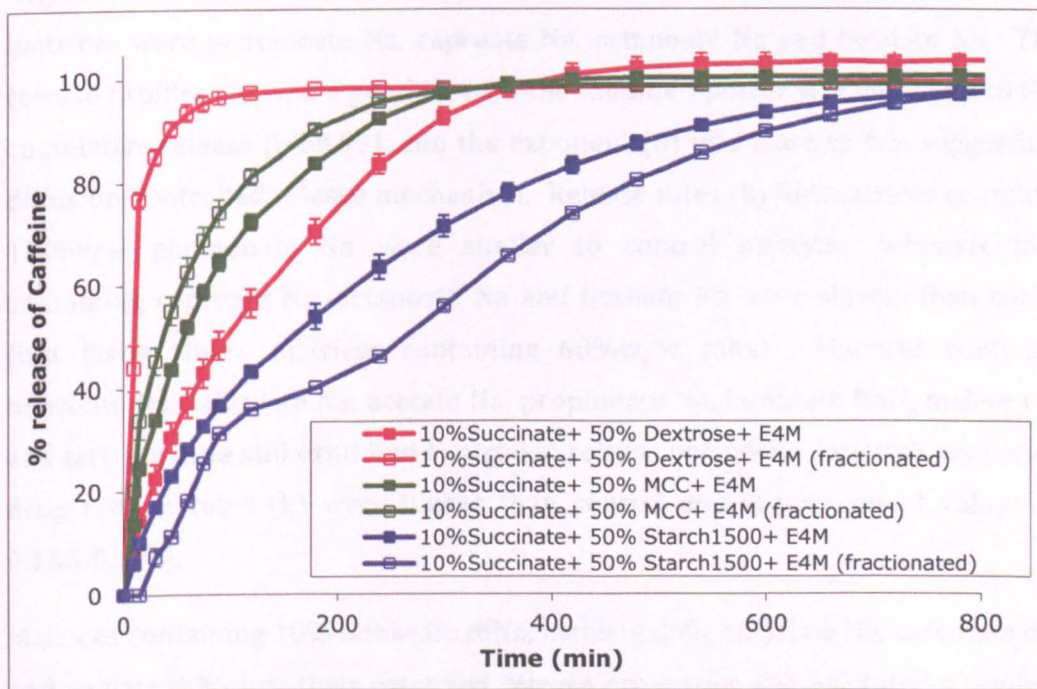


Figure 4.18 The difference of using native and sieved fraction HPMC E4M on the drug release profile of HPMC matrices containing disodium succinate. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 10%succinate diNa, qs diluents. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

4.5.3.3 The effect of 10% organic salt on drug release from HPMC matrices containing diluents

In section 4.5.2, the highest amount of organic salts (60%w/w) was used in the matrix to elicit the maximum possible effect. However, at this level it was almost impossible to differentiate the more potent salts. Therefore in this section, the effect of a lower content of organic salt (10%w/w) was investigated in matrices containing HPMC E4M (63-90 μ m fraction) with dextrose were the polymer/diluent selection from the previous section.

Table 4.14 shows the time to 80% cumulative drug release ($T_{80\%}$) and the parameters from fitting the modified power law (Ford 1987). Matrices containing 10%w/w salts exhibited the same overall trends as those containing 60%w/w salts but showed less extreme changes in their drug release profiles. For example, salts with lower potencies, such as the monovalent and hydroxylated salts, showed less burst release in their accelerated profiles.

Organic salts which maintained the controlled release characteristics of HPMC matrices were pentanoate Na, caproate Na, octanoate Na and besilate Na. Their release profiles showed a good fit with the modified power law model up to 80% cumulative release ($r^2 > 0.99$), and the exponent (n) was close to 0.5, suggesting a diffusion-controlled release mechanism. Release rates (k) for matrices containing 10%w/w pentanoate Na were similar to control matrices, whereas those containing caproate Na, octanoate Na and besilate Na were slower than control (but faster than matrices containing 60%w/w salts). Matrices containing benzoate Na, salicylate Na, acetate Na, propionate Na, fumarate NaH, malate diNa and tartrate diNa still exhibited controlled release behaviour, but with accelerated drug release rates (k) were higher than control and low exponent values ($n = 0.166-0.395$).

Matrices containing 10% fumarate diNa, maleate diNa, mesilate Na, succinate diNa and oxalate diNa lost their extended release properties and exhibited a tendency to release drug immediately although less rapidly than those containing 60% salt. If fitted to the modified power law they had very high release rate constants ($k > 46$) and low diffusional exponents ($n < 0.15$).

Organic salts	T _{80%}	k	n	r ²
<u>Control</u>				
No salt (dextrose used as a diluent)	178	9.58	0.419	0.9992
<u>Homologous series</u>				
Acetate Na	76	36.46	0.190	0.9991
Propionate Na	105	27.99	0.234	0.9996
Pentanoate Na	173	9.58	0.422	0.9990
Caproate Na	179	8.66	0.454	0.9995
Octanoate Na	184	8.38	0.449	0.9994
<u>Geometric isomerism</u>				
Fumarate diNa	54	46.73 ^(b)	0.147 ^(b)	0.9987 ^(b)
Maleate diNa	54	49.21 ^(b)	0.134 ^(b)	0.9975 ^(b)
<u>Ionisation</u>				
Fumarate Na H	60	39.43	0.185	0.9991
Fumarate diNa	54	46.73 ^(b)	0.147 ^(b)	0.9987 ^(b)
<u>Functional groups</u>				
Acetate Na	76	36.46	0.190	0.9991
Mesilate Na	44	48.48 ^(b)	0.149 ^(b)	0.9999 ^(b)
Benzoate Na	119	12.92	0.394	0.9988
Besilate Na	180	7.92	0.458	0.9979
<u>The presence of hydroxyl group(s)</u>				
Succinate diNa	18	68.83 ^(a)	0.086 ^(a)	0.9998 ^(a)
Malate diNa	61	42.25	0.166	0.9980
Tartrate diNa	91	34.75	0.192	0.9978
Benzoate Na	119	12.92	0.394	0.9988
Salicylate Na	128	12.55	0.395	0.9989
<u>The number of carboxylic groups</u>				
Acetate Na	76	36.46	0.190	0.9991
Oxalate diNa	39	57.19 ^(b)	0.108 ^(b)	0.9983 ^(b)

Table 4.14 The effect of 10% organic salts on drug release kinetics in the presence of diluents using the modified power law. Modified power law is described by Ford et al (1987) and was fitted up to 80% cumulative release. 8mm, 250mg matrices, 160MPa containing 30%HPMC E4M (63-90µm fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. T_{80%} is the time to 80% cumulative drug release. k is the kinetic constant. n is the diffusional exponent. r² is determination coefficient. (a) Drug release >80% within 30 min. (b) Drug release >80% within 1h. These fast release matrices were calculated up to 99% cumulative release.

The effect of the C-chain length of organic salts on drug release from HPMC matrices (homologous series)

Table 4.14 shows that release rate (k) and time to 80% cumulative drug release ($T_{80\%}$) values for matrices containing 10%w/w aliphatic organic salts, were in a rank order of C-chain length, as previously seen in matrices containing 60% salts (Section 4.5.2.1). However, only acetate ($f_1=52.03$, $f_2=22.19$) and propionate ($f_1=40.13$, $f_2=27.93$) significantly accelerated drug release compared with the control (Figure 4.19). This suggests that acetate and propionate might cause more osmotically driven water penetration of the matrix because osmotic pressure depends on the number of molecules available. The low molecular weight salts contain more molecules in 10% w/w than higher molecular weight salts (caproate and octanoate). Moreover, caproate and octanoate which are low potency surfactants require high amount to exhibit micellar solubilisation so that 10% may be not high enough. However, matrices containing 10%w/w octanoate sodium still formed gel layer within 10 minutes as shown in Figure 4.20(a) and (b).

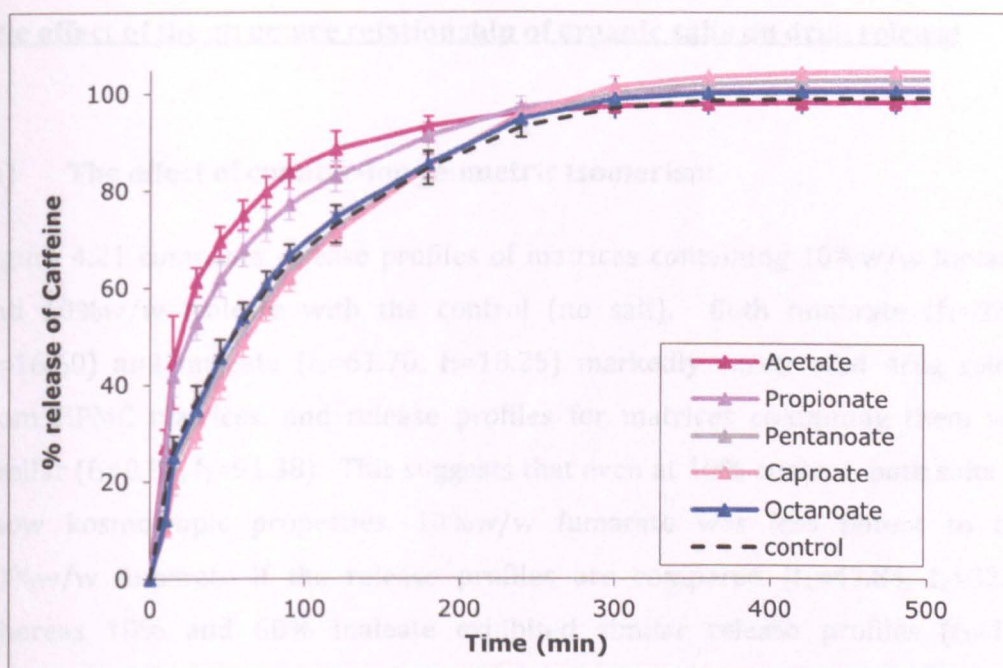


Figure 4.19 The effect of C-chain length of 10% w/w organic salts on the drug release profile of HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M (63-90 μ m fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

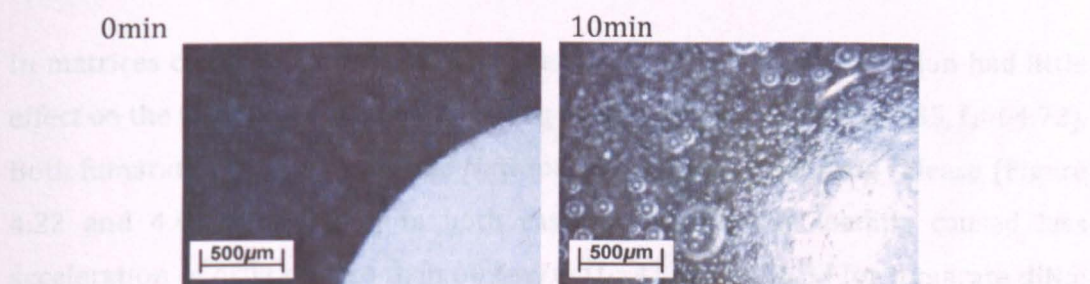


Figure 4.20(a) Microscopic photographs of HPMC matrix tablets containing 10% sodium octanoate taken from USP dissolution baskets at different times during the dissolution test. Matrices hydrated in deionised water.



Figure 4.20(b) The photograph of HPMC matrix tablets containing 10% sodium octanoate taken from USP dissolution baskets at different times during the dissolution test. Matrices hydrated in deionised water.

The effect of the structure relationship of organic salts on drug release**(a) The effect of counter-ion geometric isomerism**

Figure 4.21 compares release profiles of matrices containing 10%w/w fumarate and 10%w/w maleate with the control (no salt). Both fumarate ($f_1=87.51$, $f_2=16.60$) and maleate ($f_1=61.70$, $f_2=18.25$) markedly accelerated drug release from HPMC matrices, and release profiles for matrices containing them were similar ($f_1=0.84$, $f_2=91.38$). This suggests that even at 10% content, both salts still show kosmotropic properties. 10%w/w fumarate was less potent than 60%w/w fumarate if the release profiles are compared ($f_1=41.84$, $f_2=32.63$) whereas 10% and 60% maleate exhibited similar release profiles ($f_1=1.35$, $f_2=84.84$) as shown in Figure 4.3 and 4.21.

(b) The effect of counter-ion ionisation

In matrices containing 10%w/w salt, the degree of fumarate ionisation had little effect on the salt ability to accelerate drug release (Figure 4.22) ($f_1=4.35$, $f_2=64.72$). Both fumarate diNa and fumarate NaH markedly accelerated drug release (Figure 4.22 and 4.4). However, in both cases, 10%w/w salt loading caused less acceleration of drug release than 60%w/w ($f_1=41.84$, $f_2=32.63$ for fumarate diNa; $f_1=34.43$, $f_2=29.55$ for fumarate NaH).

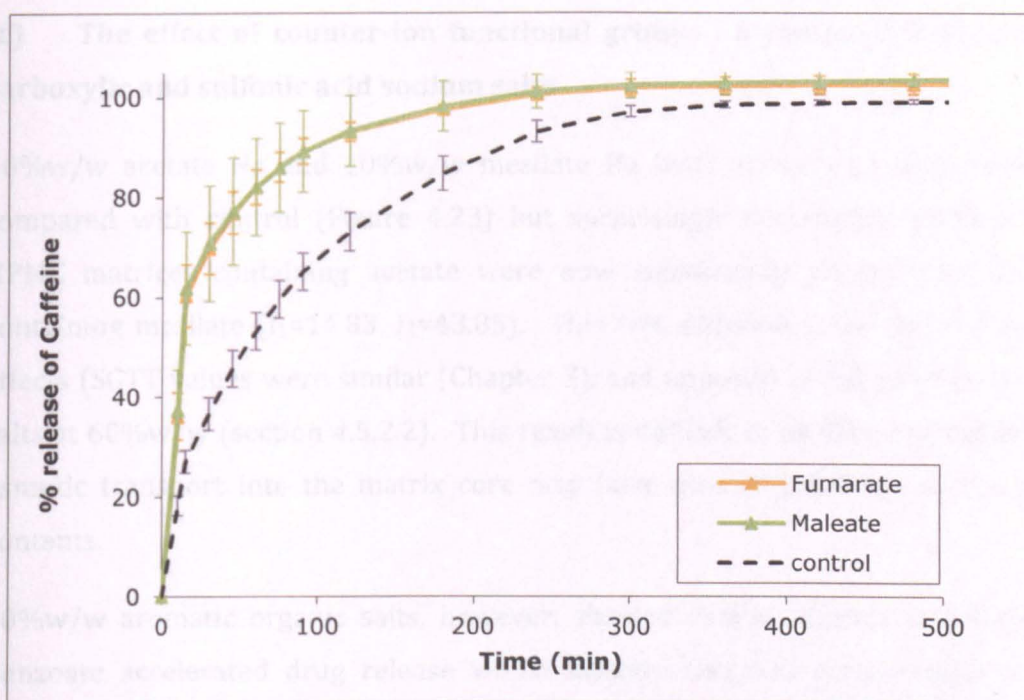


Figure 4.21 The effect of fumarate/maleate geometric isomerism (10%w/w) on the drug release profile of HPMC matrices. 8mm, 250mg matrices containing 30%HPMC E4M (63-90 μ m fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. USP I , 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

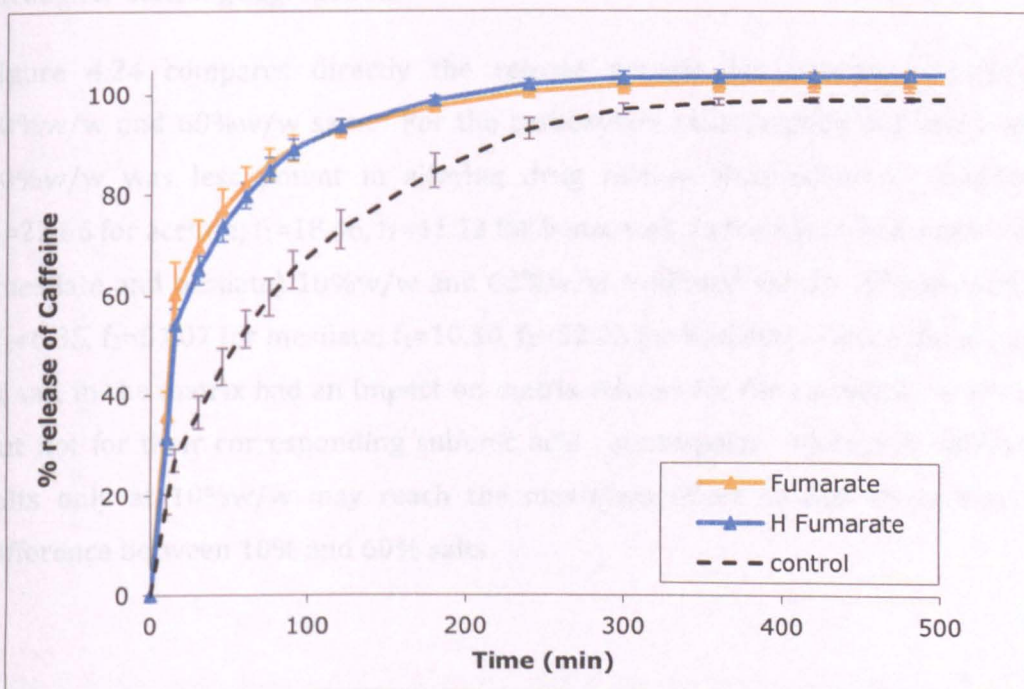


Figure 4.22 The effect of ionisation of fumarate salts (10%w/w) on the drug release profile of HPMC matrices. 8mm, 250mg matrices containing 30%HPMC E4M (63-90 μ m fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. USP I , 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

(c) The effect of counter-ion functional groups : a comparison between carboxylic and sulfonic acid sodium salts

10%w/w acetate Na and 10%w/w mesilate Na both accelerated drug release compared with control (Figure 4.23) but surprisingly the release profiles for HPMC matrices containing acetate were now significantly slower than those containing mesilate ($f_1=14.83$, $f_2=43.85$). This was different from their solution effects (SGTT values were similar (Chapter 3), and opposite to the effect of these salts at 60%w/w (section 4.5.2.2). This result is difficult to explain, and suggests osmotic transport into the matrix core may have greater influence at low salt contents.

10%w/w aromatic organic salts, however, showed similar effects to 60%w/w. Benzoate accelerated drug release whilst besilate retarded drug release with respect to the control (Figure 4.23). Besilate matrices were significantly slower than benzoate ($f_1=25.14$, $f_2=39.33$) which correlates with their effect in elevating SGTT (Chapter 3). 10%w/w benzoate may be less effective in solubilising HPMC through π -stacking aggregation.

Figure 4.24 compares directly the release profiles for matrices containing 10%w/w and 60%w/w salts. For the carboxylate salts (acetate and benzoate), 10%w/w was less potent in altering drug release than 60%w/w ($f_1=80.82$, $f_2=22.66$ for acetate; $f_1=18.46$, $f_2=41.12$ for benzoate). In the case of sulfonate salts (mesilate and besilate) 10%w/w and 60%w/w exhibited similar release profiles ($f_1=6.35$, $f_2=51.07$ for mesilate; $f_1=10.30$, $f_2=52.76$ for besilate). Hence the amount of salt in the matrix had an impact on matrix release for the carboxylic acid salts but not for their corresponding sulfonic acid counterparts. Moreover, sulfonate salts only at 10%w/w may reach the maximum effect so that there was no difference between 10% and 60% salts.

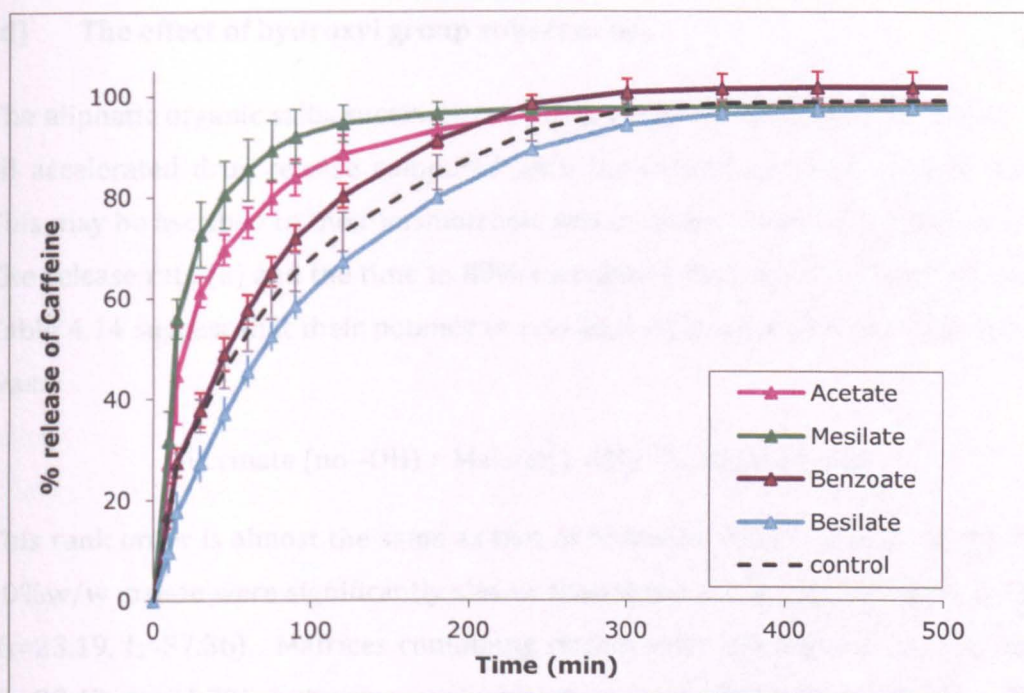


Figure 4.23 A comparison of carboxylate and sulfonate organic salts (10%w/w) on the drug release profile of HPMC matrices. 8mm, 250mg matrices containing 30%HPMC E4M (63-90 μ m fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

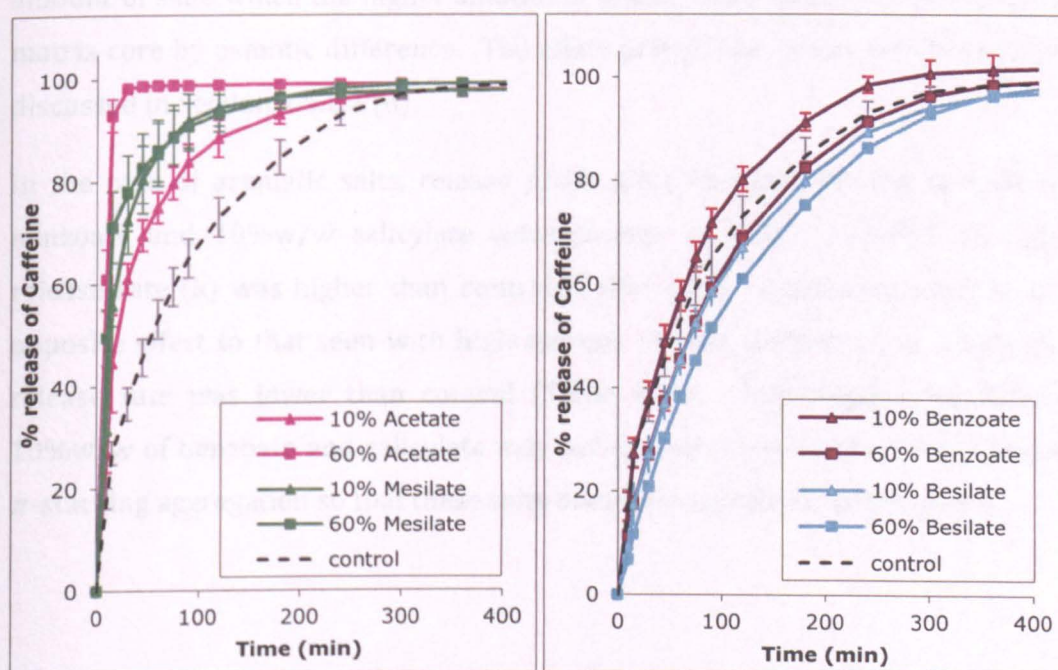


Figure 4.24 A comparison of 10%w/w and 60%w/w carboxylate and sulfonate organic salts on the drug release profile of HPMC matrices. 8mm, 250mg matrices containing 30%HPMC E4M (63-90 μ m fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

(d) The effect of hydroxyl group substituents

The aliphatic organic salts, succinate (no -OH), malate (1-OH) and tartrate (2-OH) all accelerated drug release compared with the control (no salt) (Figure 4.25). This may be ascribed to their kosmotropic action in the Hofmeister series of ions. The release rate (k) and the time to 80% cumulative drug release ($T_{80\%}$) values in Table 4.14 suggest that their potency in accelerating drug release HPMC matrices was:

$$\text{Succinate (no -OH)} > \text{Malate (1-OH)} = \text{Tartrate (2-OH)}$$

This rank order is almost the same as that of 60%w/w salts. Matrices containing 10%w/w malate were significantly slower than those containing 60%w/w malate ($f_1=23.19$, $f_2=37.36$). Matrices containing malate were dissimilar from succinate ($f_1=23.42$, $f_2=34.79$), but were equivalent to tartrate ($f_1=8.99$, $f_2=51.33$). This might arise because succinate and tartrate may have already reached their maximum effect at 10%w/w, whereas the effect of malate was affected by the amount of salts which the higher amount of malate attracted more water into the matrix core by osmotic difference. The effect of hydroxyl group substituents was discussed in Section 4.5.2.2 (d).

In the case of aromatic salts, release profiles for matrices containing 10%w/w benzoate and 10%w/w salicylate were similar ($f_1=2.21$, $f_2=83.95$), and their release rate (k) was higher than control (Table 4.14). Surprisingly this was an opposite effect to that seen with high amount of salts (60%w/w) in which their release rate was lower than control (Table 4.10). This might arise because 10%w/w of benzoate and salicylate may not enough to solubilise HPMC through π -stacking aggregation so that these salts became drug release accelerators.

(e) The effect of the number of carboxylic groups

Figure 4.26 shows release profiles for HPMC matrices containing 10%w/w acetate Na (1 COO-) and 10%w/w oxalate diNa (2 COO-). Both accelerated drug release compared with the control matrix, however, the effect of 10% salt was less potent than that of 60% salt ($f_1=80.82$, $f_2=22.66$ for acetate; $f_1=23.19$, $f_2=37.26$ for oxalate). Interestingly, when using low amount of salts, the effect of acetate and oxalate on HPMC matrices could be differentiated : drug release from oxalate matrices was statistically more quickly than acetate ($f_1=20.40$, $f_2=35.52$), and the release rate (k) of oxalate matrices was higher than acetate (Table 4.14). This corresponds to their effects on HPMC solutions in which the divalent oxalate diNa was shown to be far more potent than the monovalent acetate Na in reducing the SGTT of HPMC (Chapter 3). In matrices, the divalent oxalate will provide the more potent competitor for water, dehydrating the polymer hydration sheath, and inhibiting gel layer formation.

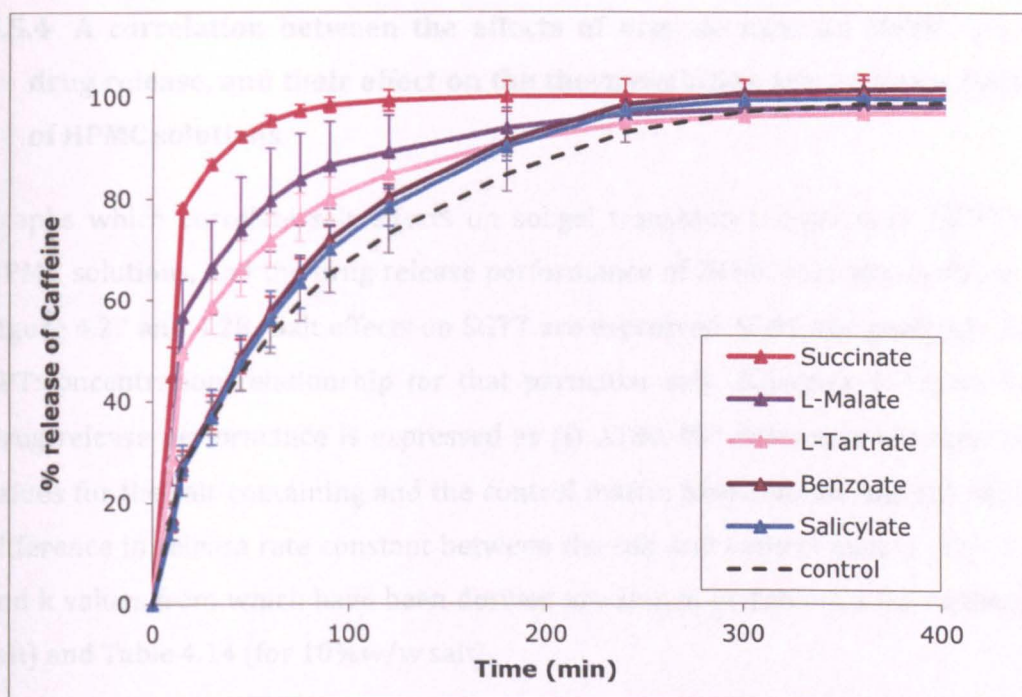


Figure 4.25 The effect of hydroxyl group substituents on the release profile of HPMC matrices (10%w/w salt). 8mm, 250mg matrices containing 30%HPMC E4M (63-90 μ m fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. USP I , 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

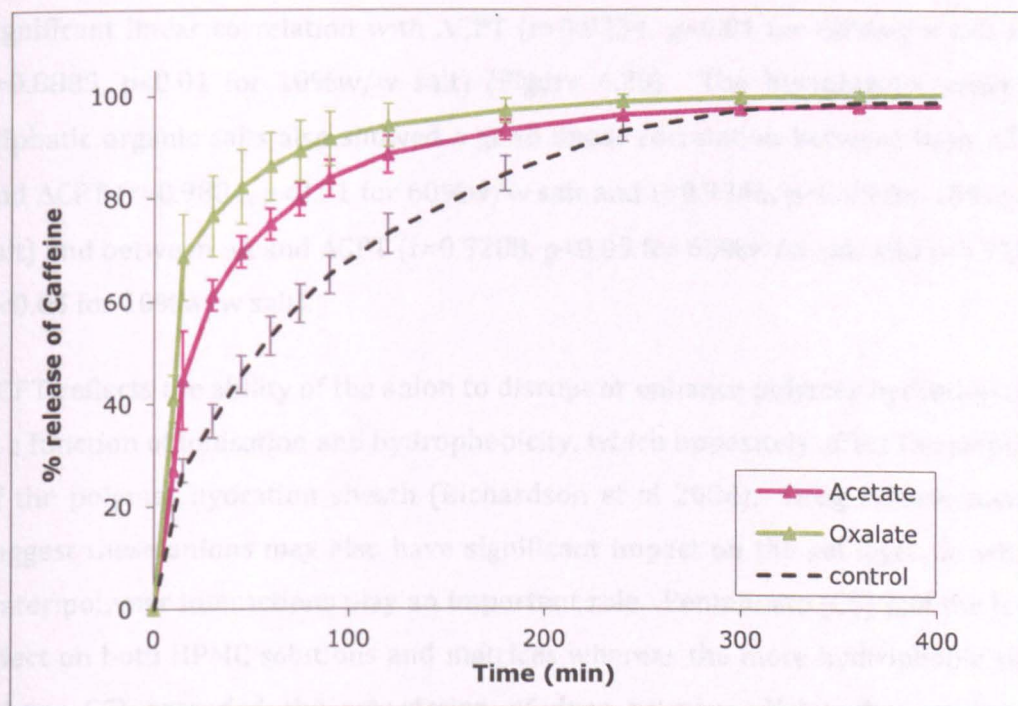


Figure 4.26 The effect of the number of carboxyl groups on the release profile of HPMC matrices (10%w/w salt). 8mm, 250mg matrices containing 30%HPMC E4M (63-90 μ m fraction), 10%caffeine anhydrous, 10% organic salt, qs dextrose. USP I , 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

4.5.4 A correlation between the effects of organic salts on HPMC matrix drug release, and their effect on the thermogelation temperature (SGTT) of HPMC solutions

Graphs which correlate salt effects on sol:gel transition temperature (SGTT) of HPMC solutions, and the drug release performance of HPMC matrices is shown in Figure 4.27 and 4.28. Salt effects on SGTT are expressed ΔCPT , the gradient of the CPT:concentration relationship for that particular salt (Chapter 3, Figure 3.4). Drug release performance is expressed as (i) $\Delta T_{80\%}$, the difference between $T_{80\%}$ values for the salt-containing and the control matrix formulations and (ii) Δk , the difference in release rate constant between the salt and control matrix. The $T_{80\%}$ and k values from which have been derived are shown in Table 4.5 (for 60%w/w salt) and Table 4.14 (for 10%w/w salt).

In the case of monovalent salts, ΔT_{80} showed a significant linear correlation with ΔCPT at 60%w/w salt ($r=0.9440$, $p<0.01$) and 10%w/w salt incorporation ($r=0.8269$, $p<0.01$) (Figure 4.27). The release rate difference (Δk) also exhibited a significant linear correlation with ΔCPT ($r=0.9254$, $p<0.01$ for 60%w/w salt and $r=0.8885$, $p<0.01$ for 10%w/w salt) (Figure 4.28). The homologous series of aliphatic organic salts also showed a good linear correlation between both ΔT_{80} and ΔCPT ($r=0.9884$, $p<0.01$ for 60%w/w salt and $r=0.9346$, $p<0.05$ for 10%w/w salt) and between Δk and ΔCPT ($r=0.9288$, $p<0.05$ for 60%w/w salt and $r=0.9156$, $p<0.05$ for 10%w/w salt).

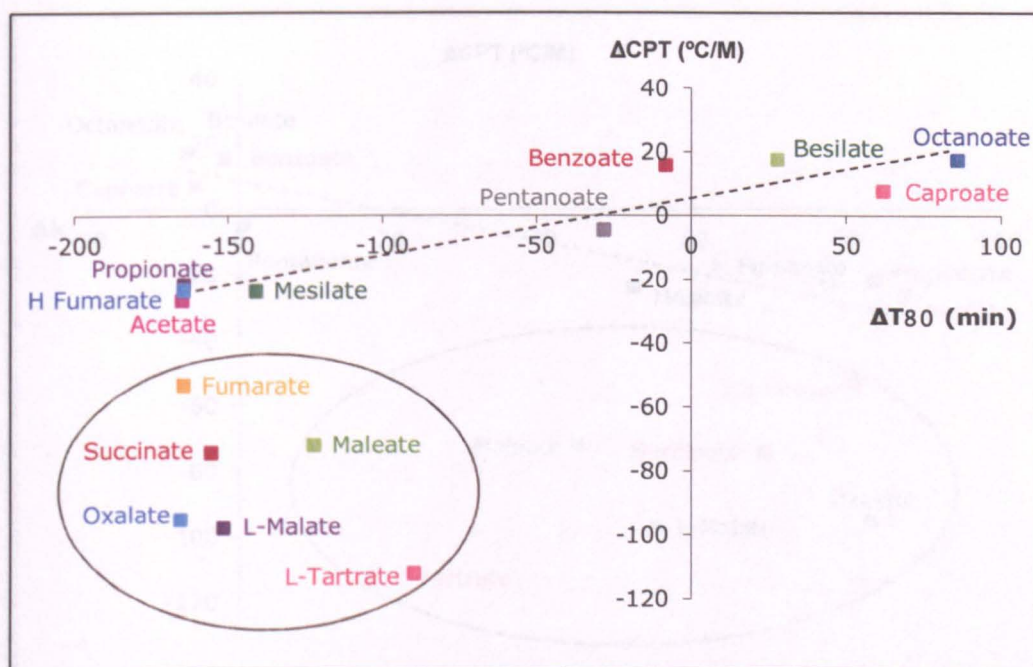
ΔCPT reflects the ability of the anion to disrupt or enhance polymer hydration and is a function of ionisation and hydrophobicity, which oppositely affect the stability of the polymer hydration sheath (Richardson et al 2006). Drug release results suggest these anions may also have significant impact on the gel layer, in which water:polymer interactions play an important role. Pentanoate (C5) had the least effect on both HPMC solutions and matrices whereas the more hydrophobic salts (above C5) extended the retardation of drug release. Using the arguments presented in the Richardson paper (2006), these salts may associate with hydrophobically substituted regions of HPMC, inducing a higher water affinity in

the polymer molecule, enhancing swelling rates leading to rapid gel layer formation, and a more quickly established gel barrier, resulting in longer extended release. In contrast, the more hydrophilic salts (below C5), would reduce water affinity of the polymer by competing for water, leading to slower gel layer formation, more extensive medium penetration of the matrix, and therefore more accelerated release properties.

Divalent anions (circled) were more potent in depressing SGTT than single valency anions, and all caused accelerated drug release, reflecting the similar effects of multivalent inorganic salts (Alderman 1984; Mitchell et al 1991; Bajwa 2006; Pygall et al 2009).

This correlation suggests that organic salts incorporated in HPMC matrices have the potential to influence drug release, in a rank order that reflects their modulation of the HPMC polymer hydration sheath in solution.

(a) 60%w/w organic salts



(b) 10%w/w organic salts

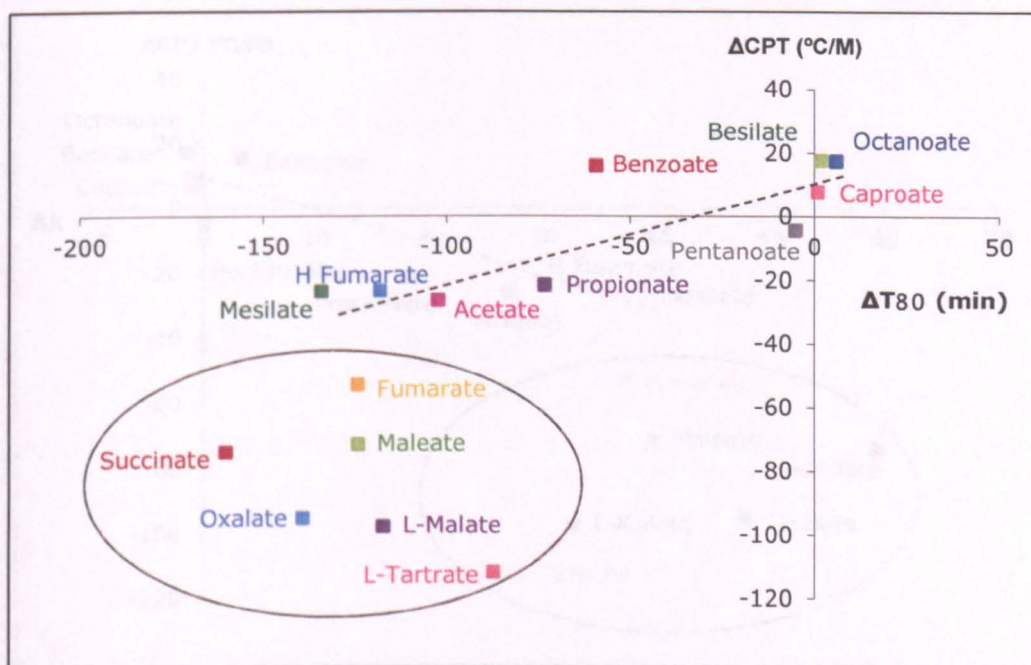
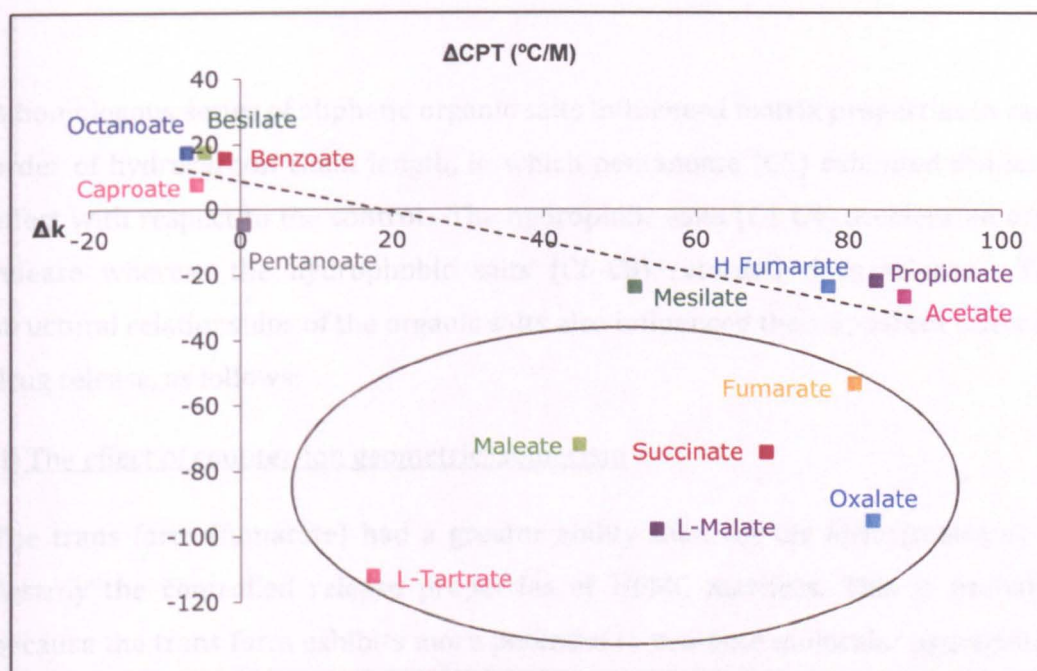


Figure 4.27 Correlation between the effect of (a) 10%w/w (b) 60%w/w organic salts on the sol-gel transition temperature (SGTT) of HPMC solutions and on the time to 80% cumulative drug release ($T_{80\%}$) of HPMC matrices. The effect on SGTT expressed as delta cloud point temperature (ΔCPT , $^{\circ}\text{C}/\text{M}$) which obtained from the gradient of CPT-salt concentration curve (Figure 3.4(a)). The effect on $T_{80\%}$ is expressed as ΔT_{80} (min) obtained from the difference between $T_{80\%}$ values for the salt-containing and the control matrix formulations (Table 4.5 and 4.14).

(a) 60%w/w organic salts



(b) 10%w/w organic salts

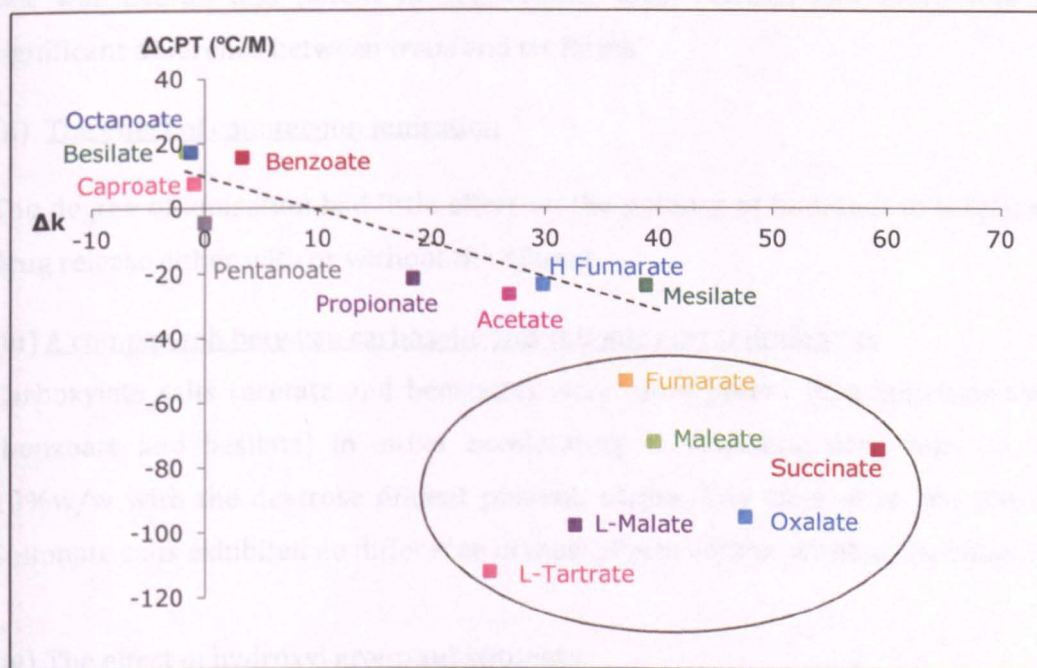


Figure 4.28 Correlation between the effect of (a) 10%w/w (b) 60%w/w organic salts on the sol-gel transition temperature (SGTT) of HPMC solutions and on the release rate (k) of HPMC matrices. The effect on SGTT expressed as delta cloud point temperature (ΔCPT , $^{\circ}C/M$) which obtained from the gradient of CPT-salt concentration curve (Figure 3.4(a)). The effect on k is expressed as Δk obtained from the difference in release rate constant between the salt and control matrix (Table 4.5 and 4.14).

4.6 Conclusions

A homologous series of aliphatic organic salts influenced matrix properties in rank order of hydrocarbon chain length, in which pentanoate (C5) exhibited the least effect with respect to the control. The hydrophilic salts (C1-C4) accelerated drug release whereas the hydrophobic salts (C6-C8) retarded drug release. The structural relationships of the organic salts also influenced their apparent effect on drug release, as follows:

(i) The effect of counter-ion geometric isomerism

The trans form (fumarate) had a greater ability than the cis form (maleate) to destroy the controlled release properties of HPMC matrices. This is probably because the trans form exhibits more potential to promote molecular aggregation of HPMC. At lower loadings of fumarate (10% w/w with a dextrose diluent) this salt was overall less potent in accelerating drug release, and there was no significant difference between trans and cis forms.

(ii) The effect of counter-ion ionisation

The degree of ionisation had little effect on the potency of fumarate to accelerate drug release either with or without the diluent.

(iii) A comparison between carboxylic and sulfonic acid sodium salts

Carboxylate salts (acetate and benzoate) were more potent than sulfonate salts (benzoate and besilate) in either accelerating or retarding drug release. At 10%w/w with the dextrose diluent present, carboxylate salts were less potent. Sulfonate salts exhibited no difference in their effects with or without the diluent.

(iv) The effect of hydroxyl group substituents

Within the aliphatic series succinate (no OH), malate (1-OH), tartrate (2-OH), the salts with hydroxyl group substituents, were less potent in accelerating drug release. This was different from their effect on HPMC solutions, in which the greater number of hydroxyl groups, the more potent in depressing the SGTT. This

may be because of differences in their molecular orientation between solutions and solids. The effects of salts on the matrix were in the same rank order with or without a diluent.

In the case of the aromatic salts, 10%w/w of benzoate and salicylate may not be enough to solubilise HPMC through π -stacking aggregation so that these salts became drug release accelerators, whereas at 60%w/w they retarded drug release.

(v) The effect of the number of carboxylic groups

Both acetate (1 COO⁻) and oxalate (2 COO⁻) accelerated drug release from HPMC matrices at 60 and 10%w/w. However, at the 10% loading oxalate was more potent in accelerating drug release, which corresponds with its greater effect on the SGTT of HPMC solutions.

The effect of matrix diluent with respect to HPMC type and the effects of organic salts

The diluents examined in this study were partially pregelatinised starch, MCC and dextrose. The latter was chosen as a soluble diluent with for minimal effect on HPMC solution SGTT.

When different diluents were incorporated into matrices containing different HPMC grades a range of effects were observed. Partially pregelatinised starch masked the effect of a potent salt (succinate Na) in all types of HPMC whereas MCC exhibited variable effects among HPMC types. Dextrose with fractionated HPMC E4M was found to be the most suitable combination to differentiate the effect of organic salts on drug release performance. With dextrose as a diluent, the effect of most organic salts was less potent either in accelerating or retarding drug release. This might be because the higher amount of salts attracted more water into the matrix core by osmotic difference.

The effect of these organic salts on the drug release performance of HPMC matrices showed a significant linear correlation with their effect on the SGTT of HPMC solutions investigated in Chapter 3. Hence the effect of organic salts incorporated in HPMC matrices, reflects their modulation of the HPMC polymer hydration sheath.

Monovalent salts containing 1 to 4 C-atoms and divalent salts lowered the SGTT of HPMC solutions, and accelerated matrix drug release (in comparison with a salt-free dextrose control). These observations are consistent with Hofmeister effects in which hydrophilic anions restructure water in the polymer hydration sheath, induce 'salting out' and suppress particle swelling and matrix gel layer formation.

Monovalent salts containing 5 to 8 C-atoms elevated SGTT and retarded matrix drug release. This suggests these salts enhance HPMC hydration possibly by interaction with polymer hydrophobic regions, by mechanisms such as micellar solubilisation and π -stacking aggregation as was described in previous studies of amino acids solution interactions with HPMC (Richardson et al 2006). It suggests that the ability of the charged ion to destabilise the polymer hydration sheath is opposed, with increasing chain length, by the ability of the hydrophobic chain to interact with and enhance polymer molecular hydration. The effects on matrix drug release also suggests that the presence of these ions impacts on water:polymer interactions which are important to the formation and diffusion barrier properties of the gel layer.

These findings provide new insights when formulating HPMC matrix tablets from caffeine and organic salts and may provide guidance for other formulations in which drug is associated with organic counterions. For example, high dose drugs with a strongly hydrophilic organic counter-ion should perhaps be avoided, whereas hydrophobic or amphipathic salts might be better candidates for incorporation into HPMC matrices, and may even improve their extended release properties.

Chapter 5

The Effect of Alkyl Sulphate Surfactants on HPMC Solutions and HPMC Matrices

5.1 Rationale

In the previous studies of the effect of organic salts on HPMC (Chapter 3 and 4), aliphatic carboxylate salts containing over 6 C-atoms were found to raise the sol:gel transition temperature and to also prolong drug release from HPMC matrices. The length of the aliphatic chain was found to be important, but the study was limited by the poor solubility of the higher chain-length salts. This suggested a further study using alkyl sulphate surfactants which have higher solubility, and which are available in a range of chain lengths. A typical example is sodium dodecyl sulphate (SDS), an alkyl sulphate surfactant containing 12 C-atoms which is widely used in pharmaceutical formulations. This chapter investigates the effects of a homologous series of alkyl sulphate surfactants on HPMC solution and matrix behaviour.

5.2 Introduction

5.2.1 Alkyl Sulphate Surfactants

Alkyl sulphate surfactants are fatty alcohol sulphates, with the general structure shown in Figure 5.1. Their surface-activity is dominated by their alkyl chain-length and counter-ion. The homologous series most commonly investigated are the sodium salts of n-alkyl sulfuric acid mono esters with an even number of carbon atoms. Alkyl sulphates with 2-8 C-atoms show typical characteristics of

organic salts, and those with 10 or more C-atoms exhibit surface active behaviour (Stache 1996). However, this surface active behaviour is changed in the presence of substances with strong hydrophobicity (Schmalstieg & Wasow 2002).

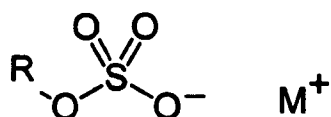


Figure 5.1 General structure of an alkyl sulphate surfactant. (R = alkyl chain)

5.2.2 Surfactants and Cellulose Ethers

The interactions between cellulose ethers and surfactants, particularly sodium dodecyl sulphate (SDS) have been widely studied. SDS is known to form micelles in water by self-assembly at concentrations above its cmc (Powney & Addison 1937; Kiraly & Dekany 2001), and addition of surfactants to a polymer solution may lead to adsorption of surfactant molecules on the polymer chain, and alter polymer solution properties. The interaction between surfactant and cellulose ethers is one of interest and there have been many attempts to clarify the interaction between them. In the early studies, SDS:EHEC (ethyl hydroxyethyl cellulose) mixture in aqueous solutions were widely investigated by a wide range of physicochemical methods including viscosity, equilibrium dialysis, steady-state fluorescence quenching, cloud point, conductometry, and H-NMR. In dilute polymer solution, an intramolecular clustering occurred with multiple mixing of the hydrophobic parts of the polymer in the same surfactant cluster. At higher polymer concentrations, surfactant clusters were shared intermolecularly, acting as 'tie points' in a 3D polymer network. Because of the adsorption of the negative-charged moiety to EHEC, uncharged polymer, the low aggregation numbers will probably create a structure similar to a polyelectrolyte (Holmberg et al 1992; Evertsson et al 1996; Holmberg & Sundelof 1996; Holmberg et al 1997; Evertsson & Nilsson 1998; Evertsson et al 1998, Singh & Nilsson 1999).

Interactions with other surfactants have been studied, for example, the dynamic surface tension of sodium deoxycholate and HPMC in aqueous solution exhibited cluster formation above CAC (Avranas & Tasopoulos 2000). The influence of counterions on the interaction between dodecyl sulfates (KDS, NaDS, LiDS) and cellulose ethers (HPMC, EHEC) has been investigated by Ridell et al (2002) who found that when Li^+ is the counterion to dodecyl sulphate, polymer-surfactant aggregates are less rigid, less densely packed and are formed at higher concentrations than with Na^+ and K^+ . The interaction between SDS and other nonionic cellulose derivatives such as hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and methyl cellulose (MC) has been studied (Wittgren et al 2005; Bosco et al 2006; Wang et al 2006). Whilst the interaction

between SDS and other anionic surfactants with HPMC have widely investigated by a wide range of techniques including viscometry, equilibrium dialysis, dye solubilisation, fluorescence, conductivity, tensiometry and cloud point. The studies all suggest that there is SDS:HPMC aggregation above the CAC. The solubilisation capacity of SDS:HPMC system is less than found for SDS:EHEC systems, and the average adsorption capacity of SDS on HPMC is found to be the order of one adsorbed amphiphile molecule per monomer unit (Hammarstrom & Sundelof 1993; Nilsson 1995; Persson et al 1996; Kulicke et al 1998; Avranas & Iliou 2003; Sovilj & Petrovic 2005; Sovilj & Petrovic 2006). A HPMC/NaCMC/SDS system was investigated by Sovilj and Petrovic (2007) and it found that SDS increased the synergistic effect between two polymers.

The effect of surfactants on drug release from HPMC matrix tablets has also been studied. Daly et al (1984) found that anionic surfactants were able to retard the release rate of chlorpheniramine maleate from HPMC matrices, while non-ionic and cationic surfactants showed no change in the release rate. Nokhodchi et al (1999; 2002) found that the theophylline release rate from HPMC matrices was accelerated by incorporated SDS whilst release of propranolol HCl from HPMC matrices decreased as the concentration of SDS was increased, which they suggested, was because SDS can form a complex with propranolol.

Cao et al (2005) found that acetaminophen release characteristics from a HPMC matrix tablet were critically controlled by the types and amounts of excipients such as surfactants, disintegrants and solubilisers incorporated. SDS can also be used in the dissolution medium for HPMC matrix tablets (Maggi et al 1996). Zeng et al (2009) found that increased SDS concentration in the dissolution medium, accelerated the nimodipine release rate from a HPMC matrix, because of both the increased solubility of nimodipine, and the increasing rate of gel erosion by SDS.

5.3 Chapter Aims and Objectives

In this chapter, the effect of SDS and its homologues on HPMC solution and matrix properties are investigated with respect to surfactant chain length. The solution studies aimed to clarify the mechanism of interaction between these alkyl sulphate surfactants and HPMC, and the matrix studies explored the influence of these surfactants on the drug release in HPMC matrices incorporating different tablet diluents.

In particular, the experimental work in this chapter, investigates the effect of alkyl sulphate surfactants on:

- The sol:gel transition temperature (SGTT), surface tension and viscoelastic properties of HPMC solutions.
- The extended release performance of HPMC matrices.

5.4 Materials and Methods

5.4.1 Surfactants

In chapter 3, organic carboxylate salts with over 6 C-atoms were found to prolong drug release from HPMC matrices, but the study was limited by the poor solubility of the longer chain organic salts. Sodium hexyl sulphate (SHS), sodium octyl sulphate (SOS), sodium decyl sulphate (SDeS), and sodium dodecyl sulphate (SDS) were selected for use in this chapter as they have higher solubility and are available on a range of interesting chain lengths. The chemical structure and cmc values of these surfactants are shown in Table 5.1. The source and batch numbers of these materials are documented in Appendix 1.

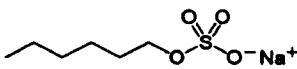
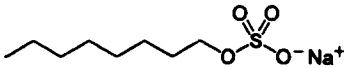
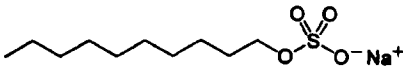
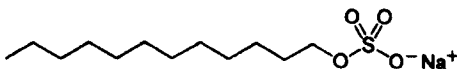
Surfactants	No. of C	cmc ^a (mM)	Structure
SHS	6	517 ^b	
SOS	8	133 ^c	
SDeS	10	33 ^d	
SDS	12	8.3 ^e	

Table 5.1 The homologous series of alkyl sulphate surfactants used in this chapter.

^a critical micelle concentration in water at 25°C, ^b Suarez et al 1999, ^c Johal 2011, ^d Kiraly & Dekany 2001, ^e Nilsson 1995

5.4.2 HPMC

HPMC USP Type 2910 (Methocel™ E4M CR Premium EP/USP) was used in this study. Full details of this material are given in Appendix 1.

5.4.3 Manufacture of HPMC solutions

The quality and source of deionized water used in solution manufacture is described in Appendix 1.

10% stock solutions were prepared by dispersing a required amount of HPMC in the hot water (>80°C) using a bench-top magnetic-stirrer with a hot plate (RCT basic, IKA Labortechnik Staufen, Janke&Kunkel GMBH&CO.KG, Germany). The dispersion was then put in an ice box to cool down to the room temperature while agitation was continued using a bench-top magnetic stirrer (KMO2 basic, IKA® Labortechnik GMBH&CO.KG, Germany). Solutions were then stored in a refrigerator at 2-8°C for at least 24 hours prior to use in order to obtain a completely hydrated solution.

To prepare solutions of 0.1 and 1% w/w HPMC, the required amount of 10% w/w HPMC stock solution was made up to volume by adding water. Solutions were stirred overnight and stored at 2-8°C for at least 24 hours prior to use.

To prepare 0.1% and 1% w/w HPMC solutions containing different concentrations of surfactants, the following method was used. HPMC and surfactant solutions were prepared separately to avoid any interactions prior to complete dissolution or hydration. The required amount of surfactants was dissolved in the remaining part of water (nine tenth of the final amount) before being incorporated into the required amount of a 10% HPMC stock solution (one tenth of the final amount). The mixed solution was stirred until homogeneous, and stored at 2-8°C for at least 24 hours prior to use.

5.4.4 Turbidimetric determination

The sol-gel transition temperature (SGTT) of HPMC solutions was determined by turbidimetry in a Cloud Point Apparatus (Medical Physics, Queen Medical Centre NHS trust, Nottingham, UK). 1%w/w HPMC solutions containing different concentrations of surfactants were used. Each sample was measured in triplicate. Full details of the method are described in Section 2.2.3.

5.4.5 Surface tension measurement

Surface tension measurements were conducted at $20 \pm 1^\circ\text{C}$ in a Profile Analysis Tensiometer (Sinterface tensiometer PAT1, Berlin, Germany) using the pendant drop method. Replicate measurements were automatically determined 100 times on each sample, and this was repeated on three separate samples of each solution. The relative standard deviations of the 100 measurements were smaller than 0.05%.

5.4.6 Density measurement

Density measurements on 0.1%w/w HPMC solutions containing surfactants were conducted by using a DMA 5000 oscillating U-tube Density Meter (Anton Paar, Graz, Austria). The density determination is based on measuring the period of oscillation of a vibrating U-shaped tube that is filled with sample and using the relationship between the period of oscillation and the density. This relation holds as long as the sample is not too viscous. The density was obtained at 20°C and mean values ($n=3$) were used subsequently in the surface tension measurements.

5.4.7 Manufacture of matrix tablets

Matrix tablets weighing 250 ± 5 mg were manufactured using a Manesty F3 single punch tablet press (Manesty, Liverpool, UK) at a compression pressure of 280MPa (within the linear range of compression pressure-hardness profile), using 8 mm flat-faced punches (I Holland, Nottingham, UK) as described in Section 2.2.7. The formulations of HPMC matrices used in this chapter are shown in Table 5.2. Tablets were prepared containing a diluent of high solubility (dextrose), an insoluble diluent (microcrystalline cellulose), a diluent of intermediate solubility (partially pre-gelatinized starch) and the 50:50 mixtures of these diluents as shown in Table 5.2 (a). Table 5.2 (b) shows the control formulations of those in Table 5.2 (a). C_A, C_B, C_C, C_D and C_E are the controls of A, B, C, D and E respectively.

5.4.8 Compression force-hardness profiles

The upper punch compression pressure was detected by a tablet compression monitor TCM1 (Copley Instruments Ltd, Nottingham, UK). Matrix tablets were sampled and tested for weight uniformity (HR-120 balance, A&D company, Limited, Japan) and crushing strength using a CT40 hardness tester (Engineering Systems, Nottingham, UK). The compression pressure was plotted against the crushing strength.

5.4.9 Dissolution determination

Drug release profiles of HPMC matrices were determined at $37 \pm 0.5^\circ\text{C}$ in 900ml of degassed deionized water using USP dissolution apparatus I (basket) at 100rpm (Dissolutest, Prolabo, France). Full details of the method are provided in Section 2.2.7.

(a) Matrices containing a surfactant

Ingredients	Grade/ Type	Weight Composition (%w/w)				
		A	B	C	D	E
Caffeine anhydrous ^a	Analytical grade	10.0	10.0	10.0	10.0	10.0
HPMC	Methocel™ E4M CR	30.0	30.0	30.0	30.0	30.0
Surfactant	SHS, SOS, SDeS, SDS	10.0	10.0	10.0	10.0	10.0
Dextrose	Meritab®	50.0	-	25.0	-	25.0
Pre-gelatinized Starch	Starch 1500®	-	50.0	25.0	-	-
Microcrystalline Cellulose (MCC)	Avicel PH102	-	-	-	50.0	25.0

(b) Control matrices

Ingredients	Grade/ Type	Weight Composition (%w/w)				
		C _A	C _B	C _C	C _D	C _E
Caffeine anhydrous ^a	Analytical grade	10.0	10.0	10.0	10.0	10.0
HPMC	Methocel™ E4M CR	30.0	30.0	30.0	30.0	30.0
Dextrose	Meritab®	60.0	10.0	35.0	10.0	35.0
Pre-gelatinized Starch	Starch 1500®	-	50.0	25.0	-	-
Microcrystalline Cellulose (MCC)	Avicel PH102	-	-	-	50.0	25.0

Table 5.2 The formulation of HPMC matrix tablets used in this chapter.^a <125 μ m sieve fraction. Full details of all materials are provided in Appendix 1.

5.4.10 Investigation of the early gel layer formation by confocal laser scanning microscopy

Early gel layer formation of HPMC matrices containing SDS in water was imaged using a confocal laser scanning microscopy. Full details of the confocal microscope, cell chamber and method are described in Section 2.2.8. 0.008%w/w Congo red solution was selected as the fluorophore based on a previous study which found that at this concentration can provide excellent microscopic detail of the gel layer (Bajwa et al 2006). Images were processed by using Image Pro Plus v6.2 software (Media Cybernetic, USA).

5.5 Results and Discussion

5.5.1 The effect of surfactants on HPMC solutions

5.5.1.1 The effect of surfactants on the surface tension of HPMC solutions

The effect of increasing HPMC concentration on the surface tension of water at 20°C is shown in Figure 5.2. This grade of HPMC reduced the surface tension of water from ~72mN/m to ~50mN/m, illustrating the known surface activity of HPMC. Figure 5.3 shows how the surface tension of water and 0.1%w/w HPMC solutions changed in the presence of the alkyl sulphate surfactants at 20°C. All surfactants in the homologous series reduced the surface tension of water and HPMC solutions and exhibited the critical micelle concentrations (cmc) and critical aggregation concentrations (CAC). The cmc and CAC values determined from this homologous series are shown in Table 5.3.

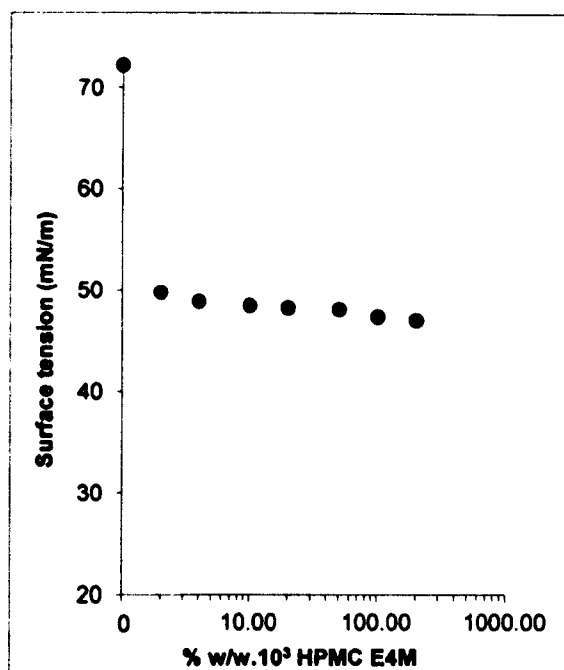
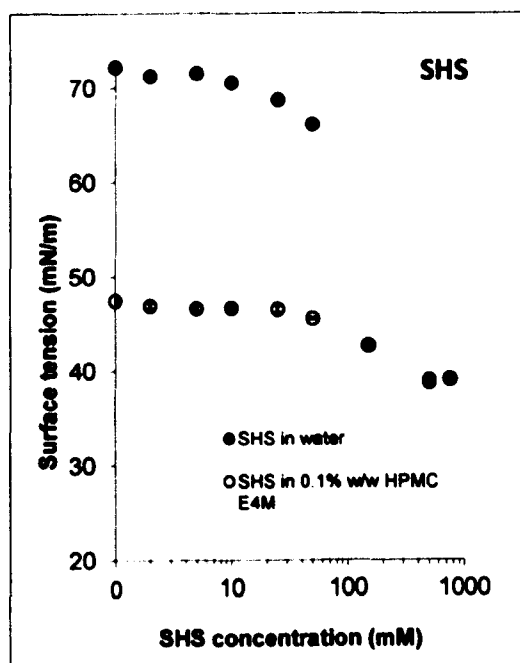


Figure 5.2 The effect of HPMC concentration on the surface tension of water at 20°C. Surface tension was measured by the pendant drop method. Mean (n=3). SD bars are smaller than the symbols.

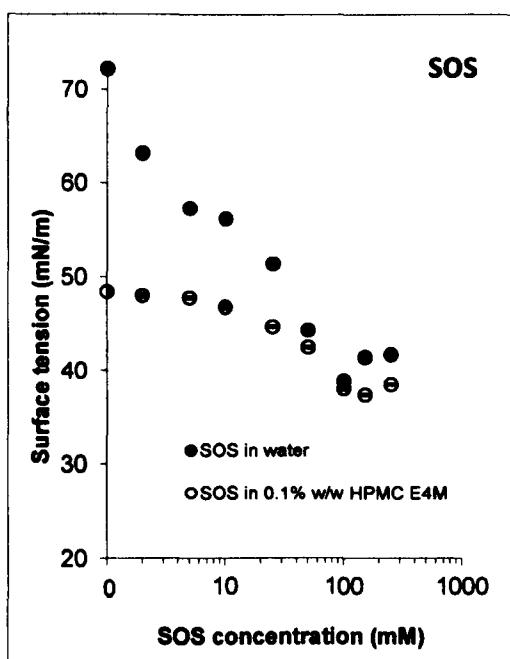
Surfactants	cmc (mM)	CAC (mM)
SHS	500	500
SOS	130	100
SDeS	40	30
SDS	8	4

Table 5.3 cmc and CAC values for a homologous series of alkyl sulphate surfactants in 0.1%w/w HPMC solution. Values were determined from the graph in Figure 5.3.

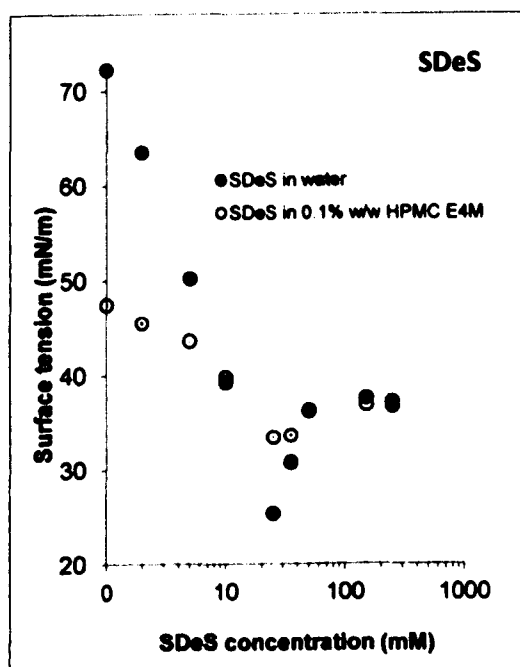
(a)



(b)



(c)



(d)

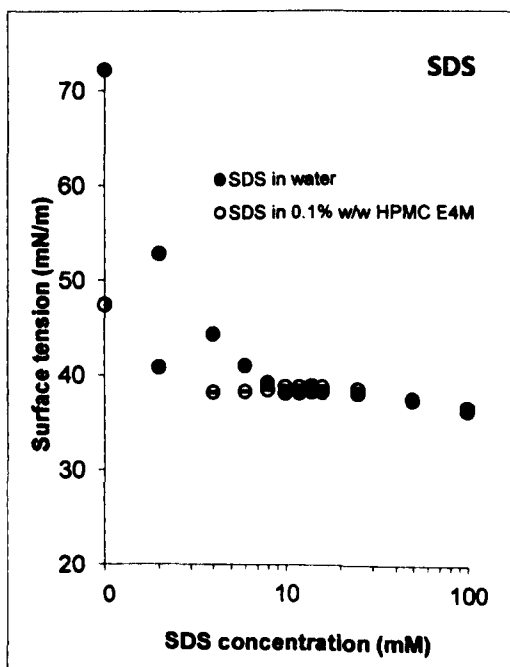


Figure 5.3 The effect of alkyl sulphate surfactant concentration on the surface tension of water and 0.1% w/w HPMC E4M CR solution at 20°C (a) SHS (b) SOS (c) SDeS (d) SDS. Surface tension was measured by the pendant drop method. Mean ($n=3$). SD bars are smaller than the symbols.

The time dependence of the reduction of the surface tension of HPMC by SHS, SOS, and SDeS has been studied by Avranas et al (2003) who found there was a lag time to a steady state value depending on the polymer concentration. Lower concentrations took a longer time to reach equilibrium surface tension values. In this study, these surfactants were measured until the surface tension profile exhibited an equilibrium value in which successive values varied by less than $\pm 0.5\%$.

Figure 5.3 and Table 5.3 show that the potency of each surfactant in the homologous series to reduce the surface tension of HPMC solution and undergo association with HPMC was in a rank order of alkyl chain length:

$$\text{SDS} > \text{SDeS} > \text{SOS} > \text{SHS}$$

The longer alkyl chain length surfactants, which are more hydrophobic, have more potential to reduce the surface tension of water and HPMC solution, and exhibited lower cmc and CAC values.

Both HPMC and surfactants are surface active and decrease surface tension, but these results also provide evidence for an interaction between HPMC and these alkyl sulphate surfactants. This is shown by the plateau phase, in which there is no further decrease of surface tension when adding the surfactants. For SHS, the onset of association requires higher surfactant concentrations than the others. It needs up to 500mM concentration for self-association and SHS-HPMC association. In the case of SOS, SDeS and SDS, the surfactant-HPMC association happened at lower concentrations than surfactant self-association in water ($\text{CAC} < \text{cmc}$). This suggests that the polymer (HPMC) can induce surfactant aggregation, and a lower concentration of surfactant is needed for solubilisation of polymer. A discussion of their effects is provided in Section 5.5.2.

5.5.1.2 The effect of surfactants on the density of HPMC solutions

Figure 5.4 shows how concentration of surfactants affected the density of water and HPMC solution. The density of water and HPMC solutions increased with increasing surfactant concentration. This can be explained through Equation 5.1.

$$\rho = \frac{m}{V} \quad \text{Equation 5.1}$$

where ρ is the density, m is the mass, V is the volume.

Interestingly, the alkyl chain length of surfactants exhibited the reverse effect from Equation 5.1 which the density of water and HPMC solutions decreased with increasing surfactant alkyl chain length. At low surfactant concentration, there was no difference in density, but at high surfactant concentration, the density varied in a rank order of chain length. This might be a result of increasing hydrophobicity of surfactant which affects their ability to form micelles with HPMC. The longer chain length surfactants can form micelles more quickly which will be discussed in more detail in Section 5.5.2. The surfactant:polymer association cause the conformation change of polymer (HPMC) in solution from the condensed coil to straight line and less compact.

The density of the solution can directly influence the surface tension of the solution determined by a pendent drop method. This shape is given by the Gauss-Laplace equation, which provides a relationship between the curvature of a liquid meniscus and the surface tension, as shown in Equation 5.2.

$$\gamma \left(\frac{1}{R_1} + \frac{1}{R_2} \right) = \Delta P_0 + \Delta \rho gh \quad \text{Equation 5.2}$$

Where γ is the surface tension, R_1 and R_2 are the main radii of curvature, ΔP_0 is the pressure difference in a reference plane, $\Delta \rho$ is the density reference, g is the acceleration due to gravity, and h is the vertical height of the drop measured from the reference plane. From Equation 5.2 and Figure 5.4, the longer chain length surfactants exhibited lower density difference ($\Delta \rho$), and hence the lower surface tension (γ) occurs as found in Section 5.5.1.1.

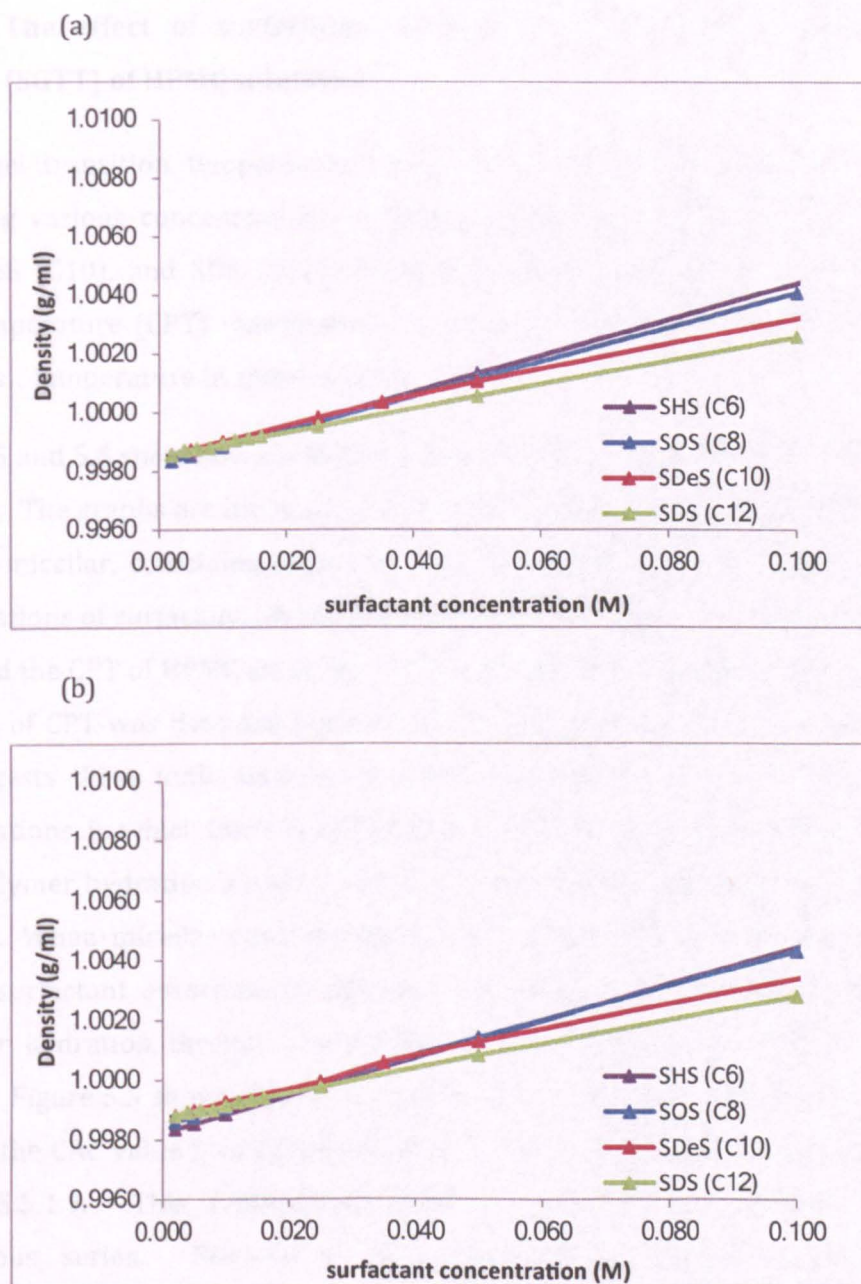


Figure 5.4 The effect of surfactant concentration on the density of (a) water, (b) 0.1%w/w HPMC solutions in the presence of a homologous series of alkyl sulphate surfactants. The density was measured at 20°C. Mean (n=3). SD bars are smaller than the symbols.

5.5.1.3 The effect of surfactants on the sol:gel transition temperature (SGTT) of HPMC solutions

The sol:gel transition temperature values (SGTT) of 1%w/w HPMC solutions containing various concentrations of alkyl sulphate surfactants (SHS (C6), SOS (C8), SDeS (C10), and SDS (C12)) were determined turbidimetrically by cloud point temperature (CPT) measurements (Section 5.4.4). SGTT is represented by cloud point temperature in these studies.

Figure 5.5 and 5.6 show how surfactant concentration influenced the CPT of HPMC solutions. The graphs are biphasic, and the effects were described as pre-micellar and post-micellar, coinciding before or after the temperature minimum. At low concentrations of surfactant (in the pre-micellar phase), alkyl sulphate surfactants depressed the CPT of HPMC solutions. After adding more surfactant, a progressive elevation of CPT was detected (this is the post-micellar phase). The lowering of CPT suggests these ionic surfactants exert a Hofmeister effect at pre-micellar concentrations, in which there is ion-mediated depletion or restructuring of water in the polymer hydration sheath around the hydrophobic, methoxyl-rich, regions of HPMC. When micellar concentrations are reached, the tensiometry suggests polymer:surfactant associations intervene, resulting in an increase in polymer molecular hydration through solubilisation of the hydrophobic regions of the polymer. Figure 5.5 shows that the critical concentration is around 6mM which is between the CAC value (4mM) and the cmc (8mM) determined by tensiometry in Section 5.5.1.1. This relationship holds for the other surfactants in the homologous series. Because of this, these alkyl sulphate surfactants at concentrations above their CAC can elevate the CPT of HPMC solutions, by association with the polymer. If this association converts the neutral HPMC into a polyelectrolyte then more water will be attracted to the polymer hydration sheath and the CPT will rise.

Figure 5.6 and 5.7 show the potential of this homologous series to elevate the CPT of HPMC solutions in the post-micellar phase. This potential is in rank order of alkyl chain length: SDS (C12) > SDeS (C10) > SOS (C8) > SHS (C6)

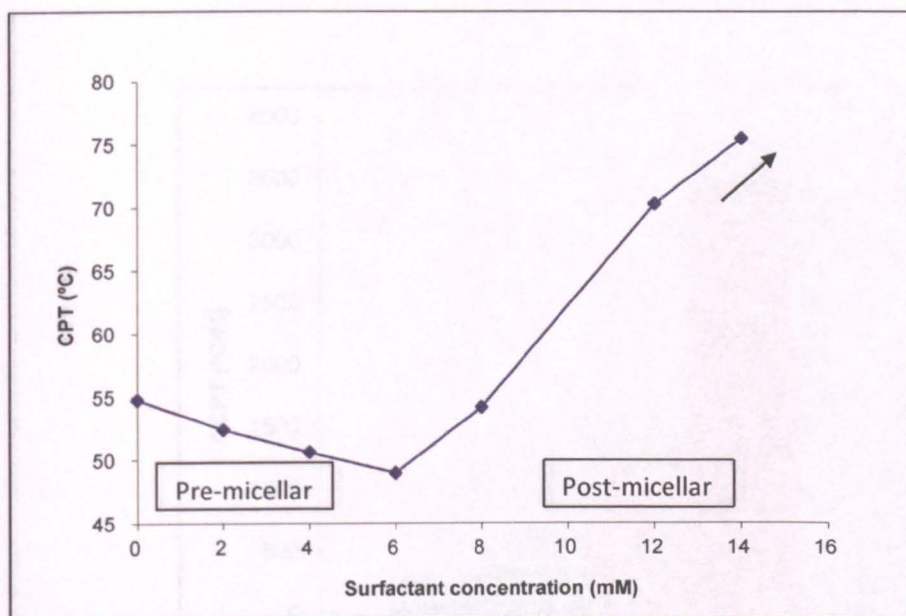


Figure 5.5 The effect of SDS concentration on the cloud point of 1%w/w HPMC E4M solutions.

Temperature ramp rate of 1.5°C/min. Mean (n=3).

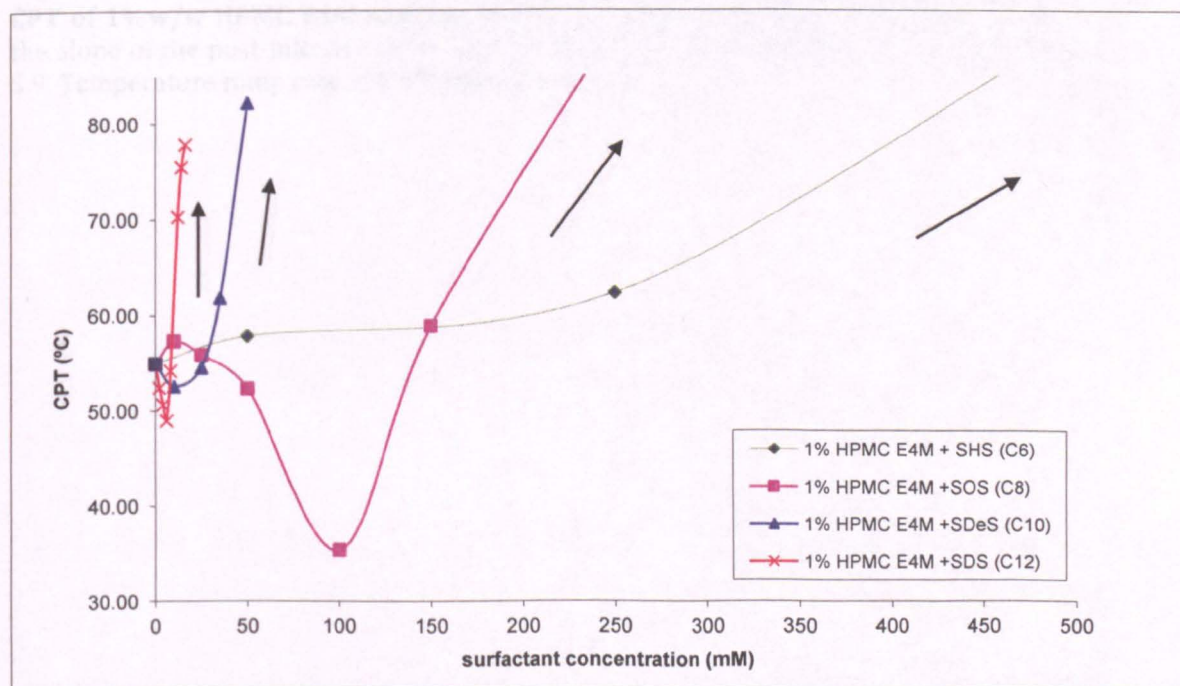


Figure 5.6 The effect of the concentration of a homologous series of alkyl sulphate surfactants on 1%w/w HPMC E4M solution.

Temperature ramp rate of 1.5°C/min. Mean (n=3).

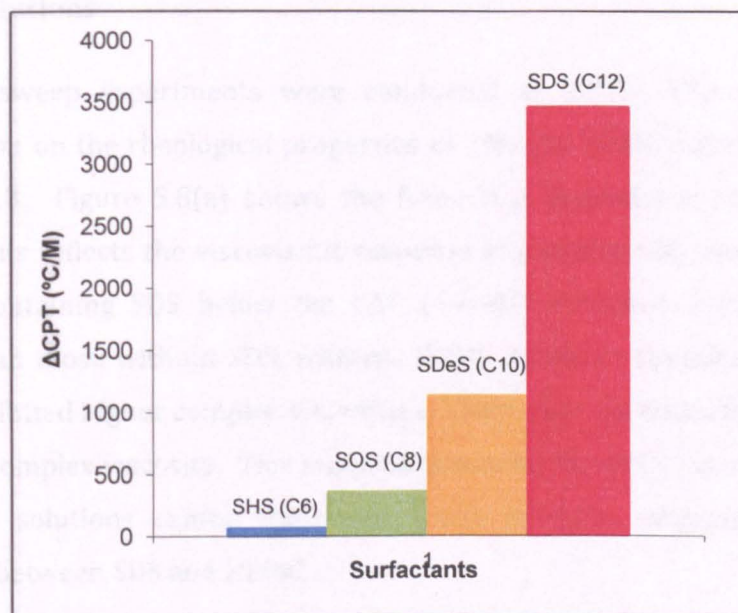


Figure 5.7 The ability of a homologous series of alkyl sulphate surfactants to elevate CPT of 1%w/w HPMC E4M solution at the post-micellar phase. ΔCPT obtained from the slope of the post-micellar curve with respect to surfactant concentration from figure 5.9. Temperature ramp rate of $1.5^{\circ}\text{C}/\text{min}$. Mean ($n=3$).

5.5.1.4 The effect of surfactants on the rheological properties of HPMC solutions

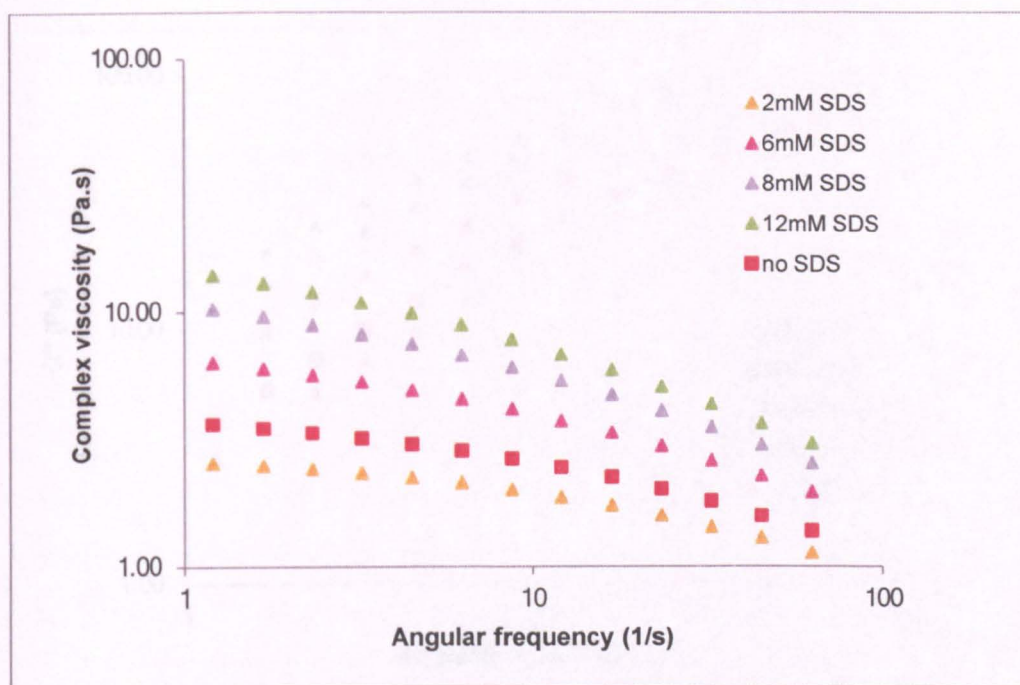
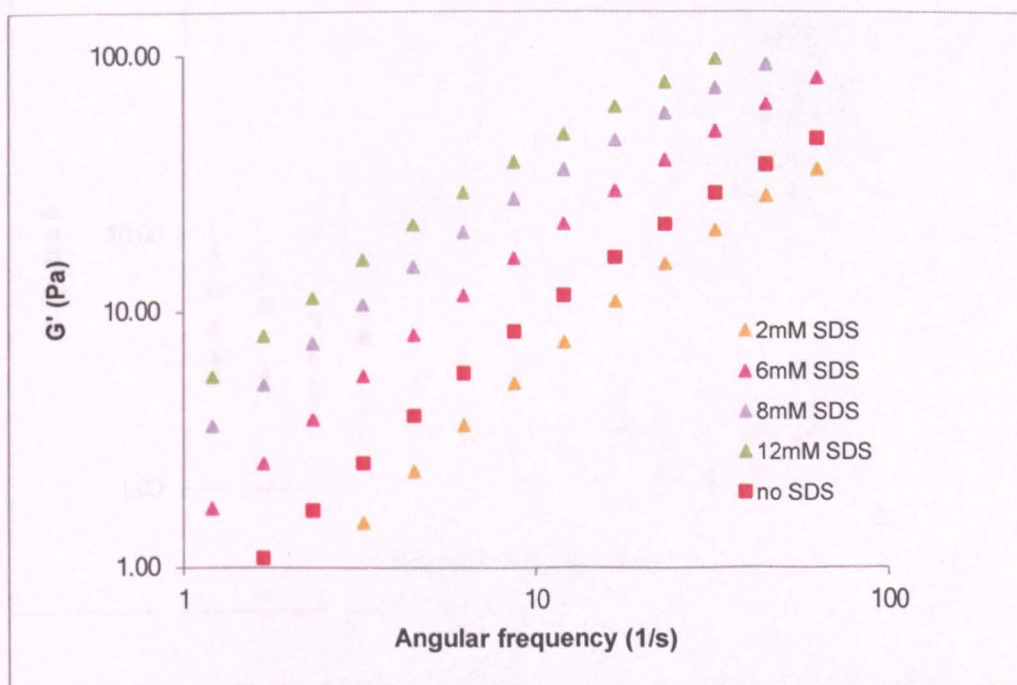
Frequency sweep experiments were conducted at 20°C. The effect of SDS concentration on the rheological properties of 2%w/w HPMC solutions is shown in Figure 5.8. Figure 5.8(a) shows the frequency dependence of the complex viscosity. This reflects the viscoelastic response of polymer-SDS mixtures. HPMC solutions containing SDS below the CAC (~4mM) exhibited a lower complex viscosity than those without SDS, whereas HPMC solutions containing SDS above the CAC exhibited higher complex viscosities. The higher the concentration of SDS, the higher complex viscosity. This suggests that with increasing concentrations of SDS, HPMC solutions exhibit more elastic-like behavior, suggesting a strong interaction between SDS and HPMC.

Figure 5.8(b) and (c) show the frequency dependence of the storage modulus (G') and loss modulus (G'') for HPMC solutions containing various concentration of SDS. In the presence of 2mM SDS (below the CAC), G' and G'' values were decreased, suggesting that low amounts of SDS suppress the viscoelastic properties of HPMC solutions. In contrast, above the CAC (6, 8, 12mM SDS), there was an increase in these mechanical moduli, showing that both elastic and viscous properties of HPMC solutions were being enhanced.

From these experiments, HPMC solutions containing SDS below the CAC appear to be behaving as a physically entangled gel with a relatively free movement of polymer chains. In contrast, HPMC solutions containing SDS above the CAC, show enhance the gel structure in both elastic and viscous properties relative to HPMC alone, and resulting from surfactant:polymer associations. The higher the SDS concentration, the the greater the enhancement of gel structure over the SDS concentrations we examined.

Tan δ values represent the ratio of G'' to G' and provide further evidence of the changes in viscoelasticity. When $\tan \delta < 1$, this indicates a shift in the sample to towards gel-like behaviour. SDS concentrations above CAC show this shift (Figure 5.8(d)).

(a) Complex viscosity

(b) Storage modulus, G' 

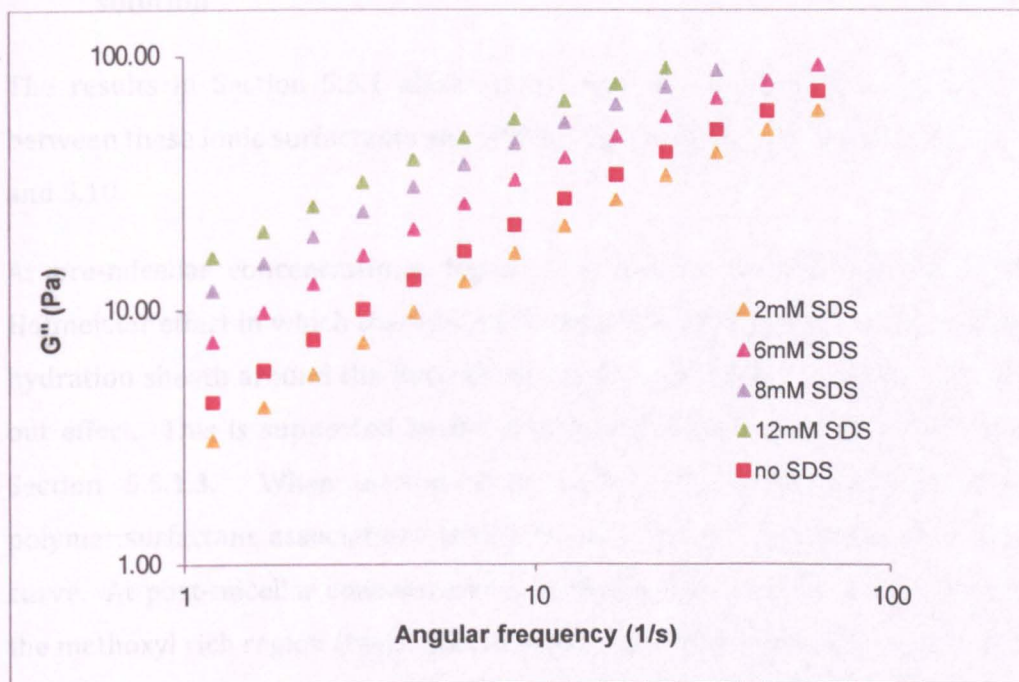
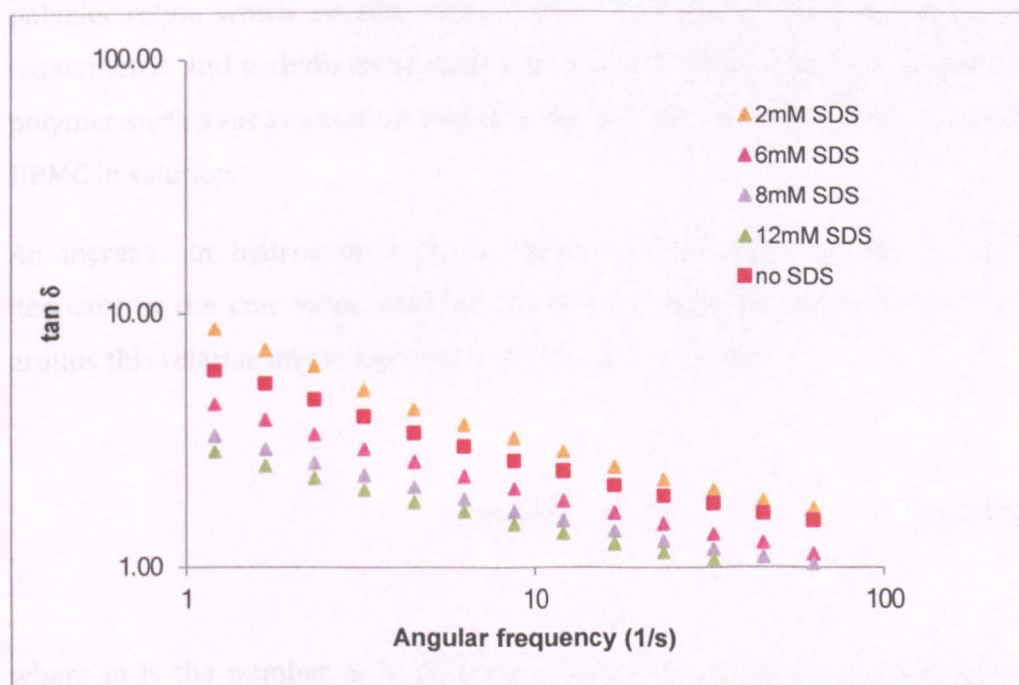
(c) Loss modulus, G'' (d) $\tan \delta$ 

Figure 5.8 The effect of SDS concentration on the frequency dependence of the (a) complex viscosity (b) G' (c) G'' and (d) $\tan \delta$ for 2%w/w HPMC solutions. Geometry = PP50. Temperature = 20°C. Strain = 1%

5.5.2 The mechanism of interaction between surfactants and HPMC in solution

The results in Section 5.5.1 allow us to postulate a mechanism of interaction between these ionic surfactants and HPMC. This scheme is illustrated in Figure 5.9 and 5.10.

At pre-micellar concentrations, Figure 5.9, ionic surfactants probably exert a Hofmeister effect in which there is ion mediated depletion of water in the polymer hydration sheath around the hydrophobic regions of HPMC, resulting in a salting-out effect. This is supported by the downward slope in the CPT curves seen in Section 5.5.1.3. When adding more surfactant to the system, increasing polymer:surfactant associations intervene and there is an inflection in the CPT curve. At post-micellar concentrations, surfactants start to form micelles around the methoxyl rich region (hydrophobic region) of HPMC, resulting in an increase in polymer molecular hydration through solubilisation of the hydrophobic regions. Moreover, the hydrophilic part of these micelles converts the neutral HPMC into a polyelectrolyte which attracts more water. This postulate is supported by the tensiometric and turbidimetric studies in Section 5.5.1.1 and 5.5.1.2 which show polymer:surfactant association evidence and a progressive increase in solubility of HPMC in solution.

An increase in hydrocarbon chain length of surfactants usually results in a decrease in the cmc value, and for compounds with identical hydrophilic head groups this relationship is expressed by the linear equation

$$\log[\text{cmc}] = A - Bm \quad \text{Equation 5.3}$$

where m is the number of hydrocarbon atoms in the chain, A is a constant for particular ionic head and B is approximately 0.3 (for a homologous series) (Prieto et al 1994; Maza et al 1999; Florence & Attwood 2009). Lunkenheimer et al (1995) also found the same relationship which differed distinctly between even and odd

number of carbon atoms. The corresponding increase in micellar size with increase in hydrocarbon chain length of surfactant is also noted (Florence & Attwood 2009). These support the investigations in Section 5.5.1 which show that increasing alkyl chain length of surfactant is associated with decreasing cmc and CAC in HPMC solutions containing surfactant. The main reason for micelle formation is to attain a state of minimum free energy so that hydrophobic part of the amphiphile will be removed from the aqueous environment by becoming the core of the micelle. A longer alkyl chain length surfactant is more hydrophobic so that the self-aggregation, polymer:surfactant association and micelle formation will occur more quickly than with a shorter chain, and exhibit a lower cmc and CAC. Moreover, the increase in alkyl chain length of surfactant raises the CPT of HPMC solutions because the longer alkyl chain surfactant has a lower cmc and CAC, leading to a greater solubilising effect on HPMC.

The postulated mechanism in Figure 5.10 also shows that when alkyl sulphate surfactants form micelles with methoxyl rich region of HPMC and convert neutral parts of the HPMC molecule into charged regions, making the polymer chain a polyelectrolyte. The increasing alkyl chain leads to a bigger size of micelle and the negative charge repulse could stretch HPMC from a condensed coil to an extended chain, resulting in the increase in viscosity of the HPMC solution. The rheological studies in Section 5.5.1.4 support this. Higher concentrations of surfactant appear to enhance rheological properties.

If surfactants make HPMC more hydrophilic and more viscous then in matrix tablets the gel layer might form more quickly and the layer may be more viscous. This could result in drug release from matrix tablets showing greater retardation.

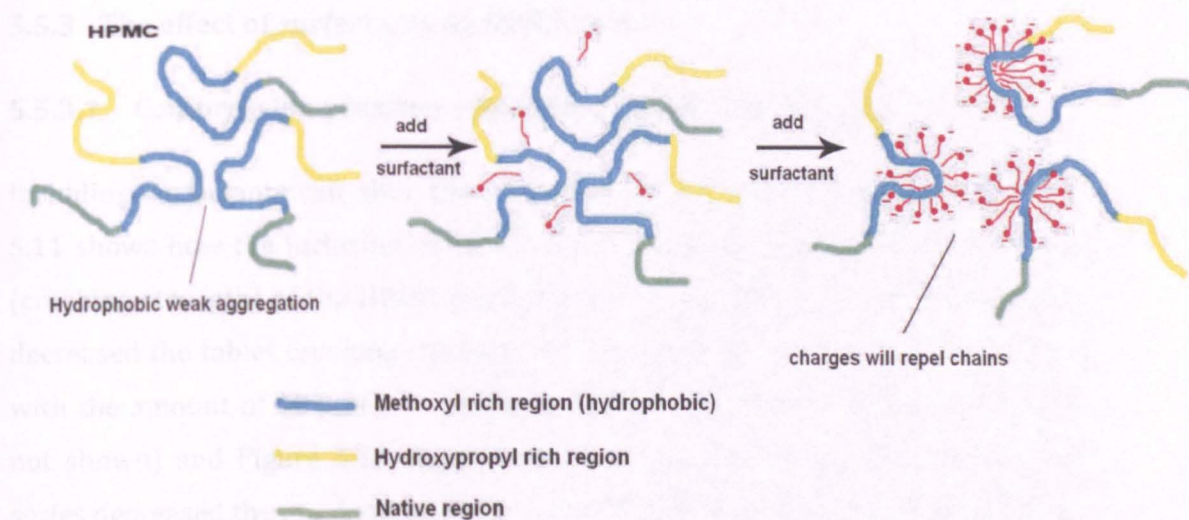


Figure 5.9 Illustration of the mechanism between HPMC and surfactants

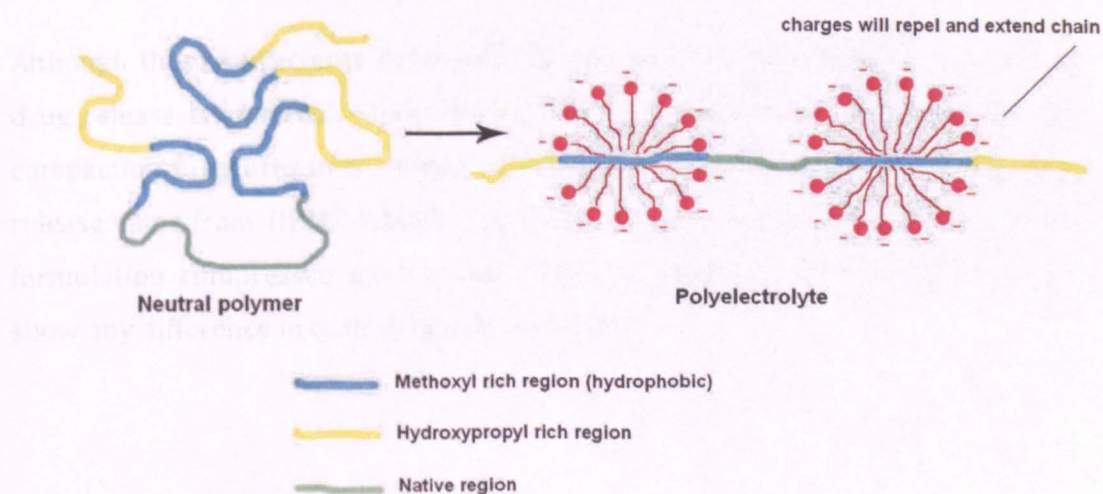


Figure 5.10 Illustration of the postulated interaction mechanism between HPMC and long chain surfactants

5.5.3 The effect of surfactants on HPMC matrices

5.5.3.1 Compression pressure – hardness profile of HPMC matrix tablets

Including surfactants can alter the properties of the tablet compact, and Figure 5.11 shows how the inclusion of SDS in our formulation influenced the hardness (crushing strength) of the HPMC matrix tablet. The presence of SDS in the tablet decreased the tablet crushing strength, but this effect did not appear to correlate with the amount of SDS added. Other surfactants exhibited similar effects (data not shown) and Figure 5.12 shows how different members of the homologous series decreased the crushing strength of HPMC matrix tablets. There appeared to be no dependency on chain length although the potential of 10% SHS to decrease the crushing strength appeared slightly less than 10% SOS, 10% SDeS or 10% SDS. These effects suggest that all the surfactants investigated reduced interparticulate bonding within the tablet structure but without any concentration dependency in the range studied.

Although these surfactants decreased the hardness of the tablets, little effect on drug release is expected. Daly et al (1984) amongst others have reported that compaction pressures in the range of 50-200 MPa do not significantly alter drug release rates from HPMC tablets. Appendix 4 shows that HPMC matrices of our formulation compressed over a wide range of pressures (80-320MPa) did not show any difference in their drug release profiles.

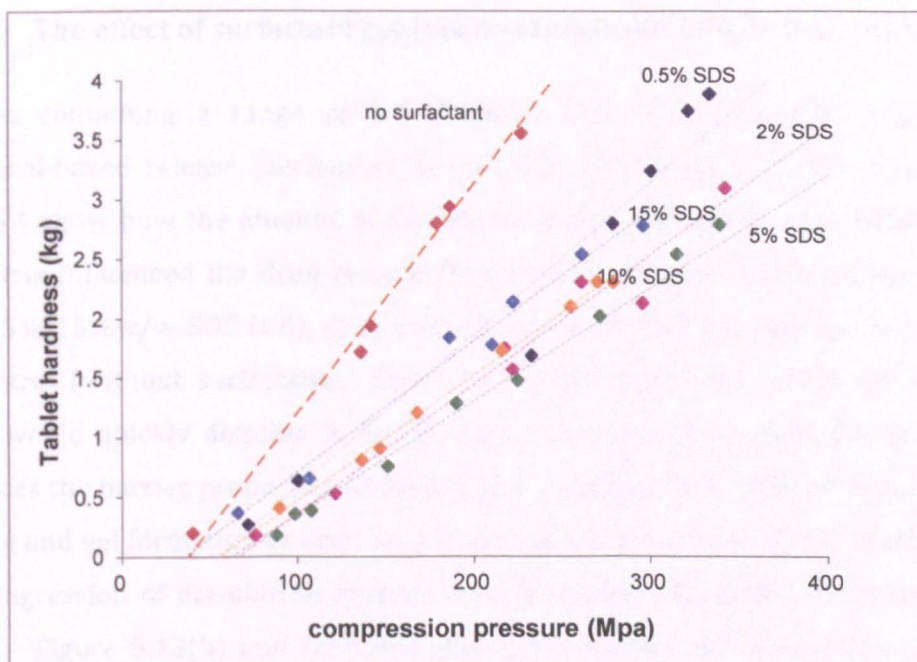


Figure 5.11 Compression pressure - hardness profiles for HPMC matrix tablets containing the different amounts of SDS

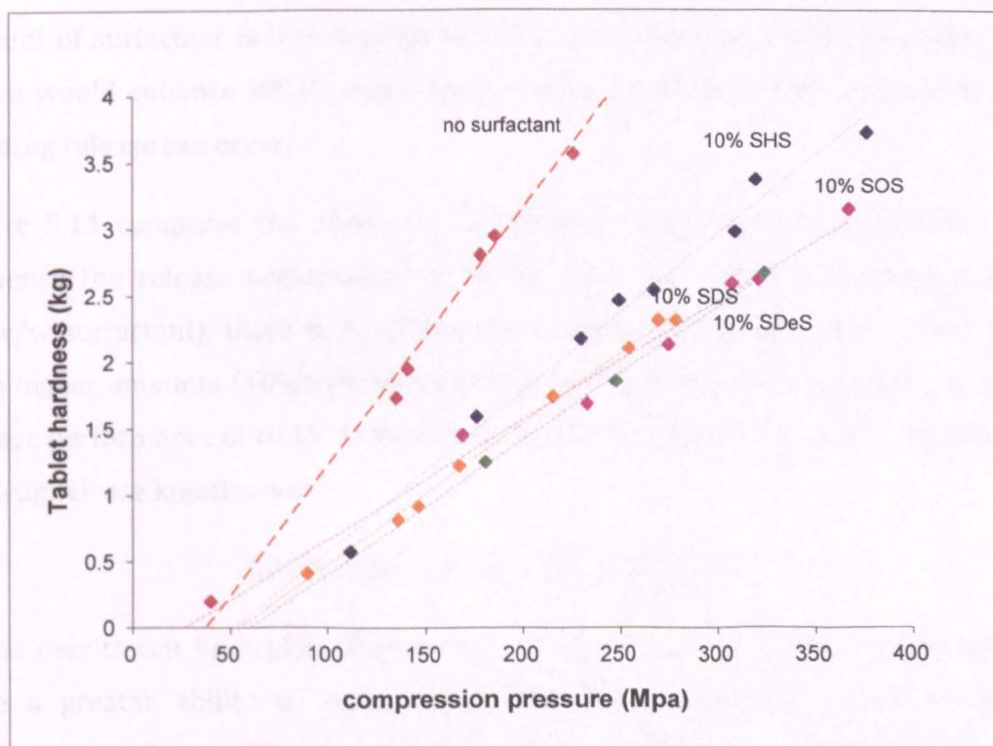


Figure 5.12 Compression pressure - hardness profiles for HPMC matrix tablets containing 10%w/w of different alkyl sulphate surfactants

5.5.3.2 The effect of surfactant content on the matrix drug release profile

Matrices containing a range of 0.5-15%w/w SOS, SDeS and SDS exhibited diffusional-based release mechanism ($n \sim 0.4-0.5$) (Table 5.4). Figure 5.13 and Table 5.4 show how the amount of the alkyl sulphate surfactant incorporated in the matrix influenced the drug release time profile. Figure 5.13(a) shows that with 0.5%-15%w/w SOS (C8), drug release was accelerated in comparison with the control (without surfactant). SOS is a soluble ingredient, which we might expect would quickly dissolve in the gel layer. The results suggests it somehow influences the barrier properties of the gel layer, possibly by suppressing polymer swelling and gel formation as seen with other salts (Bajwa et al 2006), leading to faster ingress of dissolution medium into the tablet and acceleration of drug release. Figure 5.13(b) and (c) show that low amounts (0.5-5%w/w) of SDeS (C10) and SDS (C12) all accelerated the drug release. In contrast, 15%w/w SDeS, 10% and 15%w/w SDS retarded drug release compared with the control as seen with their slower release rate (k) (Table 5.4). These results suggest that if the amount of surfactant is high enough to induce the surfactant:HPMC aggregation, which would enhance HPMC solubility and viscosity, then greater retardation of the drug release can occur.

Figure 5.14 compares the ability of the different alkyl sulphate surfactants to influence the release performance of HPMC matrices. With low amounts (0-5%w/w surfactant), there is no difference between these surfactants. However with higher amounts (10%w/w surfactant or more), their ability to influence the release performance of HPMC is more clearly differentiated. The rank order effect on drug release kinetics was

$$\text{SOS (fastest)} > \text{SDeS} > \text{SDS (slowest)}$$

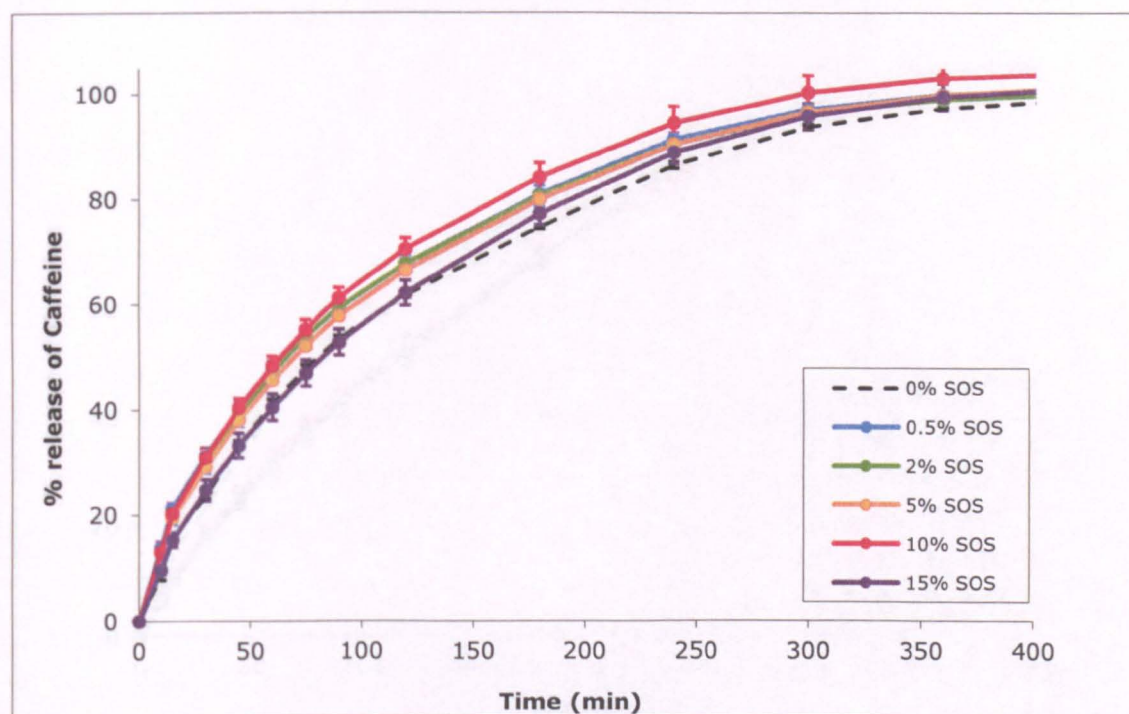
These results can be explained in that the longer alkyl chain length surfactants have a greater ability to induce surfactant:polymer association and micelle formation (as discussed in Section 5.5.2), and can enhance the solubility of HPMC, leading perhaps to quicker gel layer formation and a more viscous gel layer, resulting in greater retardation of drug release.

Surfactants	$T_{80\%}$	K	n	r^2
<u>Control</u> (no surfactant)	206	6.65	0.477	0.9982
<u>SOS</u>				
0.5%	176	10.43	0.401	0.9990
2%	177	9.82	0.414	0.9988
5%	180	9.06	0.427	0.9991
10%	162	9.67	0.425	0.9990
15%	194	6.60	0.480	0.9987
<u>SDeS</u>				
0.5%	176	10.37	0.402	0.9990
2%	179	9.07	0.428	0.9992
5%	173	9.08	0.412	0.9992
10%	195	7.60	0.451	0.9978
15%	204	6.02	0.488	0.9969
<u>SDS</u>				
0.5%	184	9.87	0.407	0.9989
2%	178	8.11	0.450	0.9993
5%	174	8.97	0.430	0.9979
10%	222	4.02	0.557	0.9978
15%	218	3.68	0.568	0.9970

Table 5.4 The effect of surfactant content on drug release kinetics using the modified power law. Modified power law is described by Ford et al (1987) and was fitted up to 80% cumulative release. 8mm, 250mg matrices, 280MPa containing 30% HPMC E4M, 10% caffeine anhydrous, x% surfactant, qs. Dextrose. $T_{80\%}$ is the time to 80% cumulative drug release. k is the kinetic constant. n is the diffusional exponent. r^2 is determination coefficient.

Note: SHS was not included in this section because of the limited amount of material available (The product was being no longer manufactured)

(a)



(b)

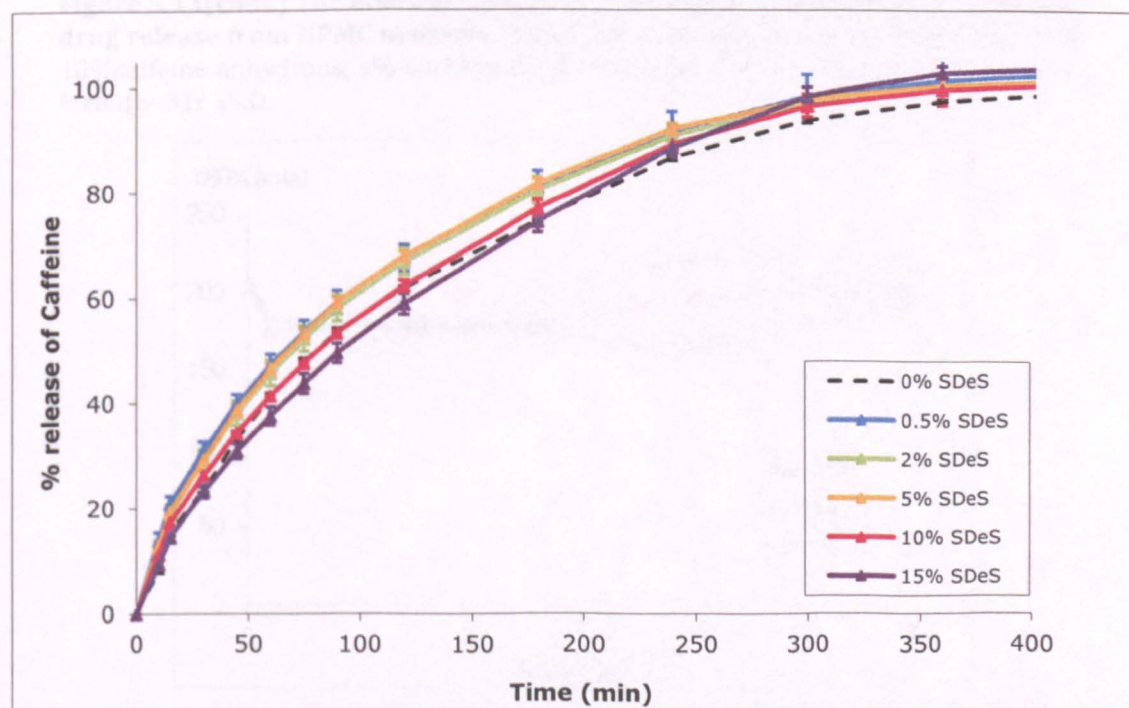


Figure 5.13 The effect of surfactant content (a) SOS, (b) SDeS or (c) SDS on drug release from HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, x% surfactants, qs Dextrose. USP I, 100rpm, 37°C in water. Mean(n=3)± 1S.D.

(c)

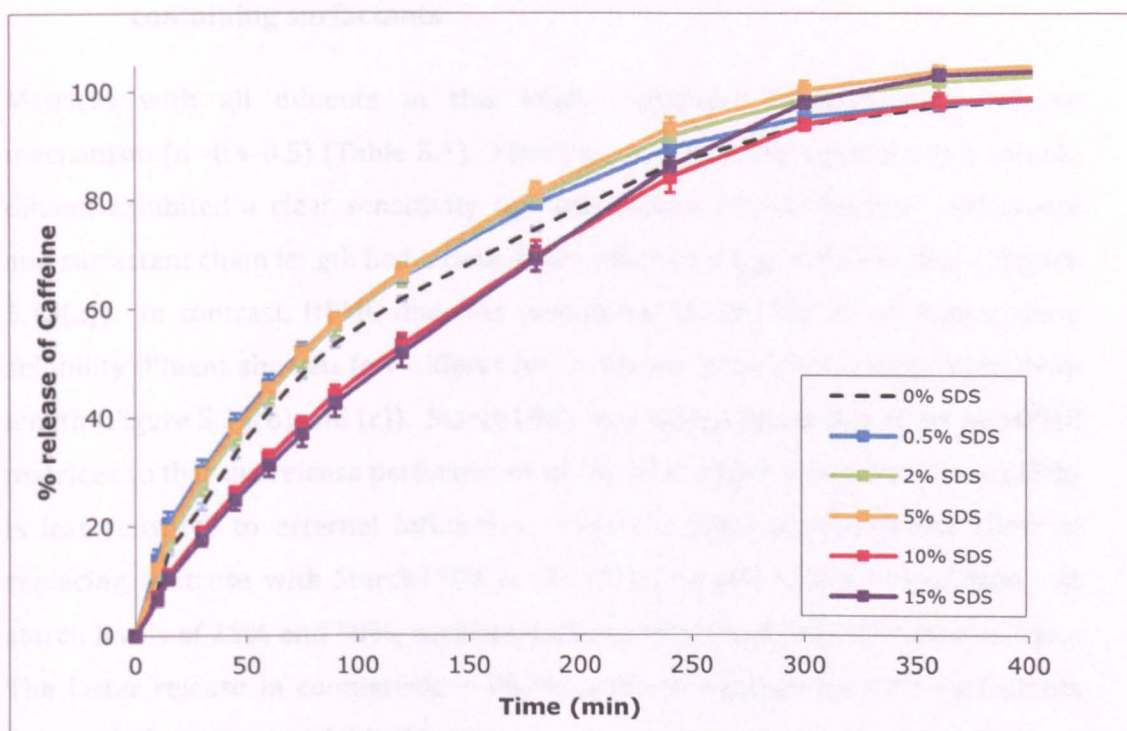


Figure 5.13(cont.) The effect of surfactant content (a) SOS, (b) SDeS or (c) SDS on drug release from HPMC matrices. 8mm, 250mg matrices contain 30%HPMC E4M, 10%caffeine anhydrous, x% surfactants, qs Dextrose. USP I, 100rpm, 37°C in water. Mean(n=3)± 1S.D.

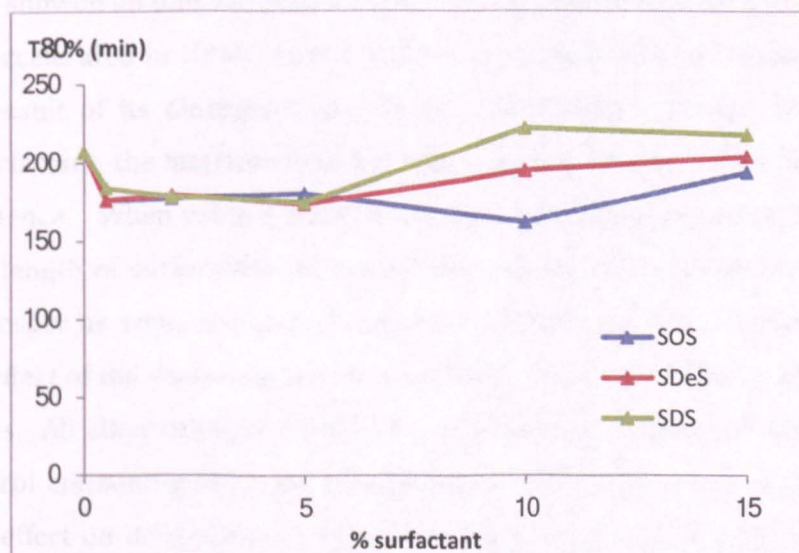


Figure 5.14 The effect of surfactant content on T80% drug release. 8mm, 250mg Matrices contain 30%HPMC E4M, 10%caffeine anhydrous, x% surfactant, qs Dextrose. USP I, 100rpm, 37°C in water. Mean(n=3)± 1S.D. T80% is the time to 80% drug release.

5.5.3.3 The effect of tablet diluents on drug release from HPMC matrices containing surfactants

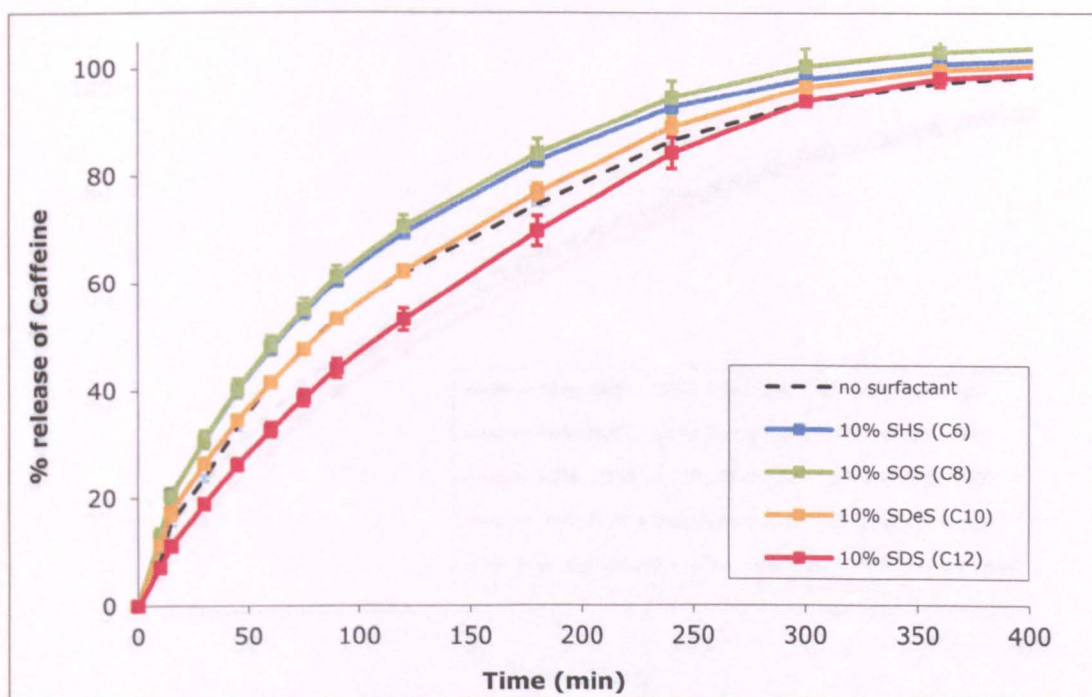
Matrices with all diluents in this study exhibited diffusion-based release mechanism ($n \sim 0.4-0.5$) (Table 5.5). Matrices incorporating dextrose as a soluble diluent exhibited a clear sensitivity to the presence of incorporated surfactants and surfactant chain length had a rank order effect on drug release kinetics (Figure 5.15(a)). In contrast, HPMC matrices containing Starch1500 as an intermediate solubility diluent showed few differences in release profile with surfactant chain length (Figure 5.15(b) and (c)). Starch1500 may have a protective effect on HPMC matrices so that the release performance of HPMC matrices containing Starch1500 is less sensitive to external influences. Figure 5.16(a) illustrates the effect of replacing dextrose with Starch1500 in the HPMC matrix tablet formulation. At starch levels of 25% and 50%, surfactant chain length had little influence on $T_{80\%}$. The faster release in comparison with the control suggests that the surfactants were merely acting as soluble diluents.

Matrix behaviour was also different when the tablet diluent was wholly insoluble (microcrystalline cellulose, MCC) or was a 50:50 mixture of MCC and dextrose. The control showed an unusual result. Figure 5.15(d) shows how drug release was extremely accelerated in HPMC matrix tablets containing MCC as a diluents : this may be a result of its dintegrant properties. By adding 10%w/w of an alkyl sulphate surfactant, the matrices then became retarded, but the alkyl chain length had no influence. When using a 50:50 mixture of MCC and dextrose, the effect of alkyl chain length of surfactants on the release profile can be differentiated in a same rank order as when using dextrose alone (Figure 5.15(e)). Figure 5.16(b) shows the effect of the replacing dextrose with MCC102 in the HPMC matrix tablet formulations. All alkyl sulphate surfactants retarded drug release in comparison with a control containing MCC and no surfactant. Surfactant chain length had a rank order effect on drug release in tablets containing 25%w/w MCC, but not in those containing 50%w/w MCC. This suggests that using soluble diluents either alone or mixture with insoluble can differentiate the effect of alkyl chain length of surfactants more clearly than using only insoluble diluents.

Formulations	SHS				SOS				SDeS				SDS			
	T80	k	n	r ²	T80	k	n	r ²	T80	k	n	r ²	T80	k	n	r ²
A (dextrose)	167	9.83	0.419	0.9992	166	9.67	0.425	0.9990	192	7.60	0.451	0.9978	222	4.02	0.557	0.9978
B (Starch1500)	339	4.37	0.504	0.9996	332	4.18	0.513	0.9996	324	3.93	0.525	0.9993	317	3.59	0.543	0.9996
C (Dextrose+ Starch1500)	258	5.15	0.500	0.9994	250	5.06	0.505	0.9994	256	5.10	0.501	0.9990	266	4.03	0.540	0.9994
D (MCC)	294	6.12	0.457	0.9997	298	5.67	0.471	0.9990	271	6.49	0.454	0.9994	283	4.04	0.534	0.9994
E (Dextrose+ MCC)	164	11.38	0.390	0.9985	168	10.78	0.400	0.9991	196	8.63	0.428	0.9984	248	4.57	0.520	0.9977

Table 5.5 The effect of diluents on drug release kinetics of HPMC matrices containing surfactants using the modified power law. Fitted up to 80% cumulative release. Modified power law is described by Ford et al (1987). The detail of formulation A, B, C, D and E is in Table 5.2. T_{80%} is the time to 80% drug release. k is the kinetic constant. n is the diffusional exponent. r² is coefficient of determination.

(a) dextrose Starch1500 (1:1)



(b) Starch1500

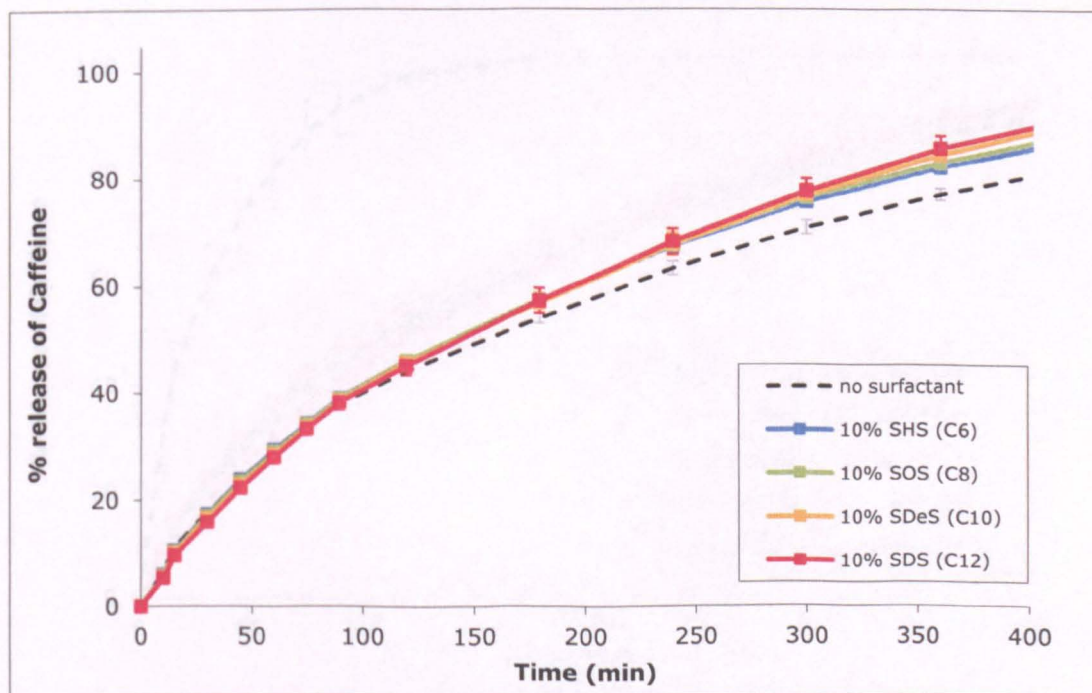
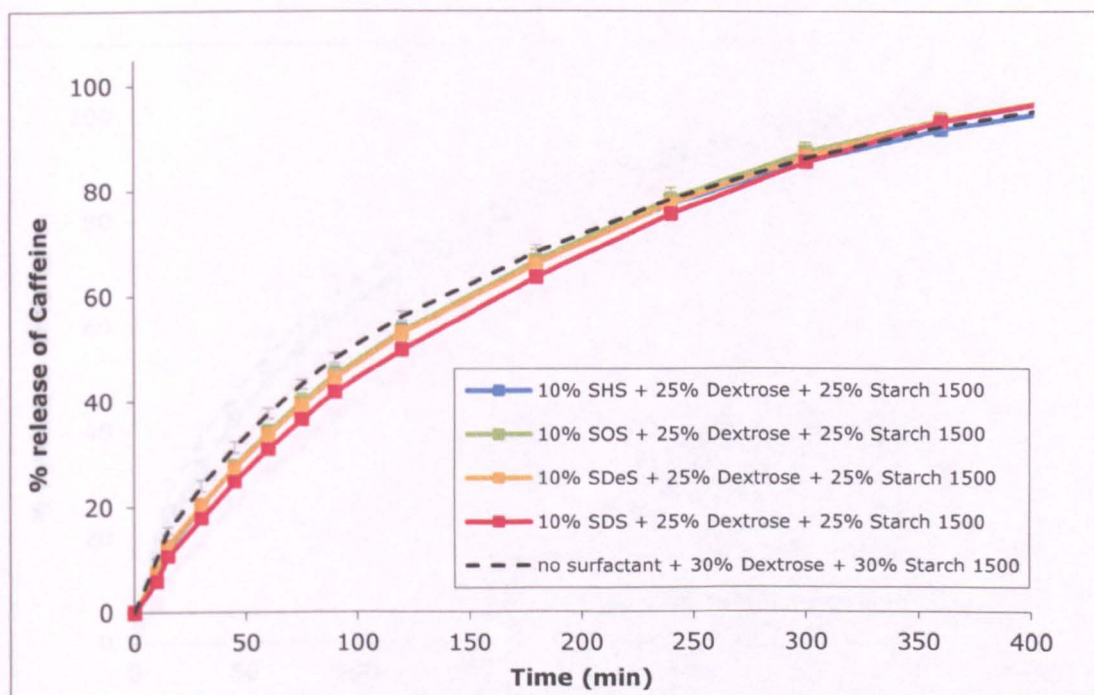


Figure 5.15 The effect of a homologous series of alkyl sulphate surfactants on the drug release profile of HPMC matrices containing (a) dextrose, (b) Starch1500, (c) dextrose: Starch1500 (1:1), (d) MCC or (e) dextrose:MCC (1:1) as diluents. 8mm, 250mg Matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 10% surfactants, qs diluents. USP I, 100rpm, 37°C in water. Mean(n=3)± 1S.D.

(c) dextrose: Starch1500 (1:1)



(d) MCC

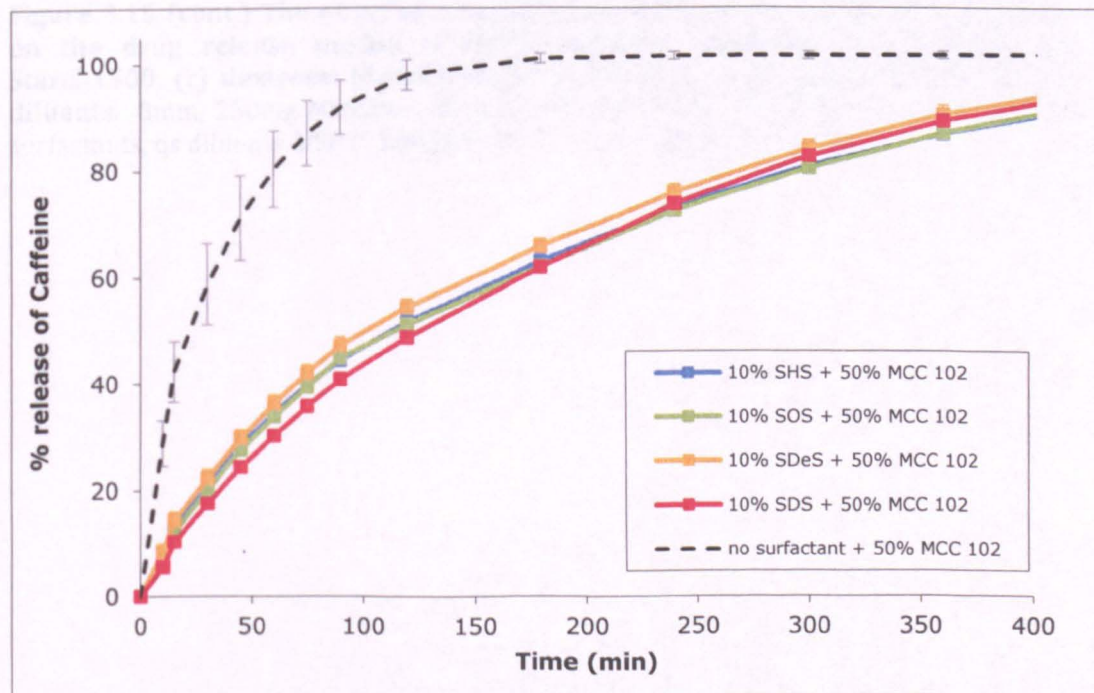


Figure 5.15 (cont.) The effect of a homologous series of alkyl sulphate surfactants on the drug release profile of HPMC matrices containing (a) dextrose, (b) Starch1500, (c) dextrose: Starch1500 (1:1), (d) MCC or (e) dextrose:MCC (1:1) as diluents. 8mm, 250mg Matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 10% surfactants, qs diluents. USP I, 100rpm, 37°C in water. Mean(n=3)± 1S.D.

(e) dextrose:MCC (1:1)

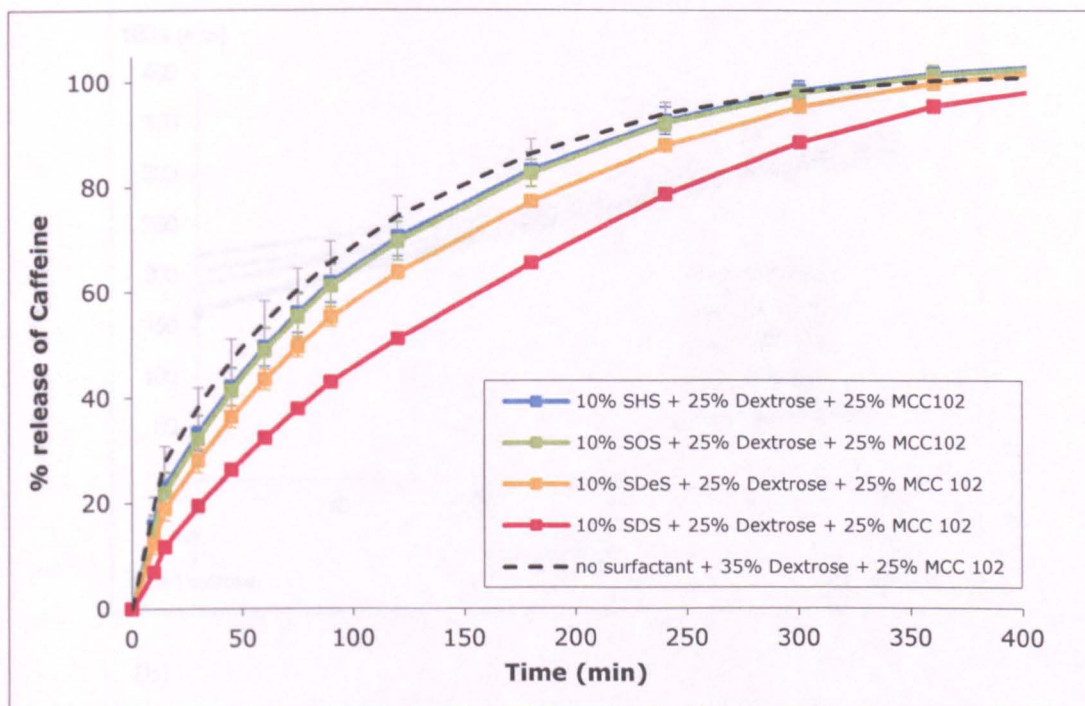
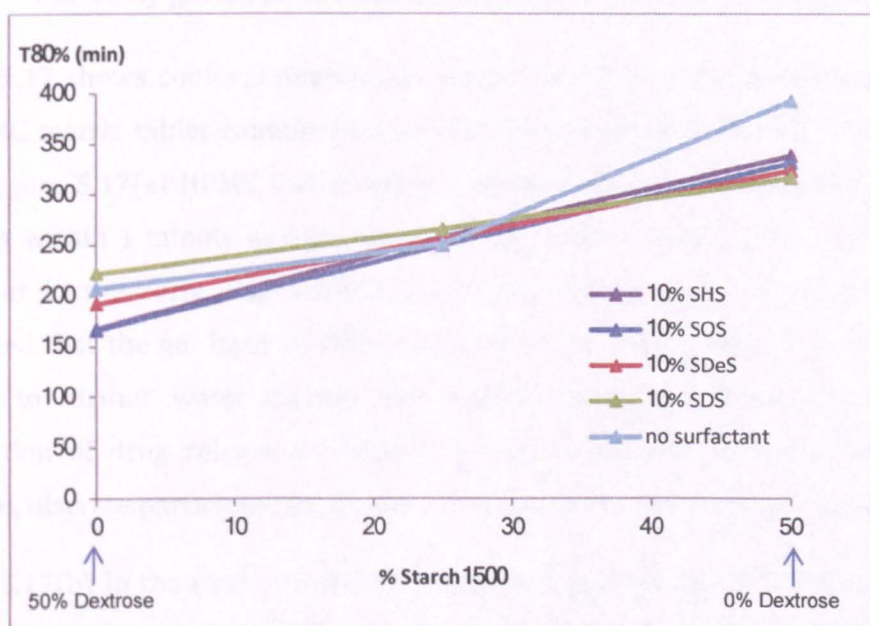


Figure 5.15 (cont.) The effect of a homologous series of alkyl sulphate surfactants on the drug release profile of HPMC matrices containing (a) dextrose, (b) Starch1500, (c) dextrose: Starch1500 (1:1), (d) MCC or (e) dextrose:MCC (1:1) as diluents. 8mm, 250mg Matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 10% surfactants, qs diluents. USP I, 100rpm, 37°C in water. Mean(n=3)± 1S.D.

(a)



(b)

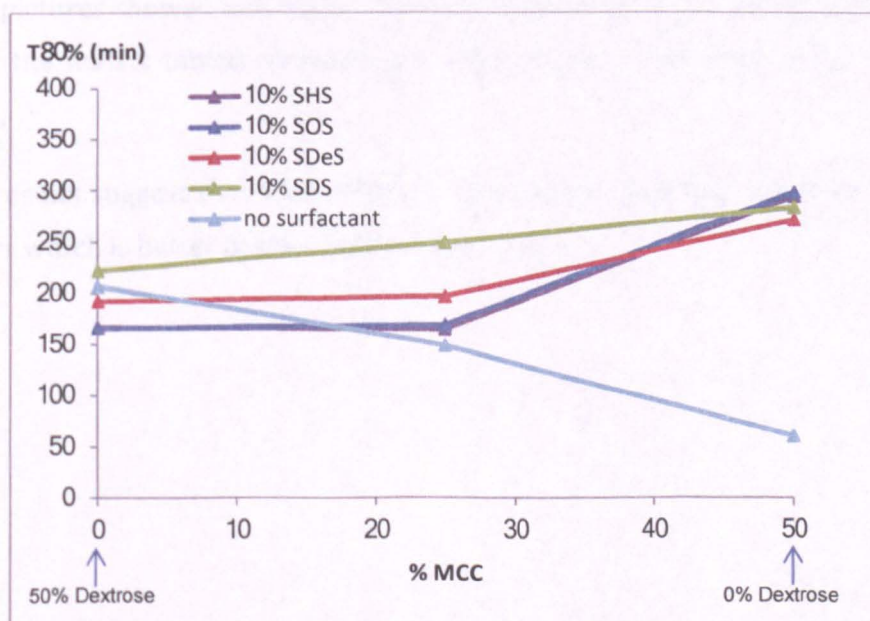


Figure 5.16 The effect of replacing Dextrose with (a) Starch1500 or (b) MCC on the drug release profile of HPMC matrices containing surfactants. 8mm, 250mg Matrices contain 30%HPMC E4M, 10%caffeine anhydrous, 10% surfactant, 50% diluents. USP I, 100rpm, 37°C in water. Mean(n=3)± 1S.D. T80% is the time to 80% drug release.

5.5.3.4 The early gel layer development of HPMC matrices containing SDS

Figure 5.17 shows confocal microscopy images of early gel layer development in an HPMC matrix tablet containing a soluble diluent (dextrose) with and without SDS. Figure 5.17(a) HPMC matrix tablets containing dextrose showed significant swelling within 1 minute and gel layer formed within 3-5 minutes. The gel was thick but in the early stages there were deep channels in the gel layer. This suggested that the gel layer of HPMC matrices containing dextrose is not a good barrier to further water ingress and might explain the relatively moderate retardation of drug release in HPMC matrices using dextrose as a diluent. In addition, discrete particles were visible in the gel layer during the entire test.

Figure 5.17(b) In the case of HPMC matrix tablets containing 10% SDS (also with dextrose as a diluent), HPMC matrices showed a similar pattern. However the final gel layer (at 15 minutes) was more uniform and coherent in appearance, and the earlier pictures showed less major channelling of the gel layer. In addition the dry core of the matrix tablets showed less water ingress compared to the dextrose control.

These results suggest that with 10%w/w SDS, HPMC matrices may form a better gel layer which is better barrier to the water ingress.

(a) Control 0%w/w SDS

(b) 10%w/w SDS

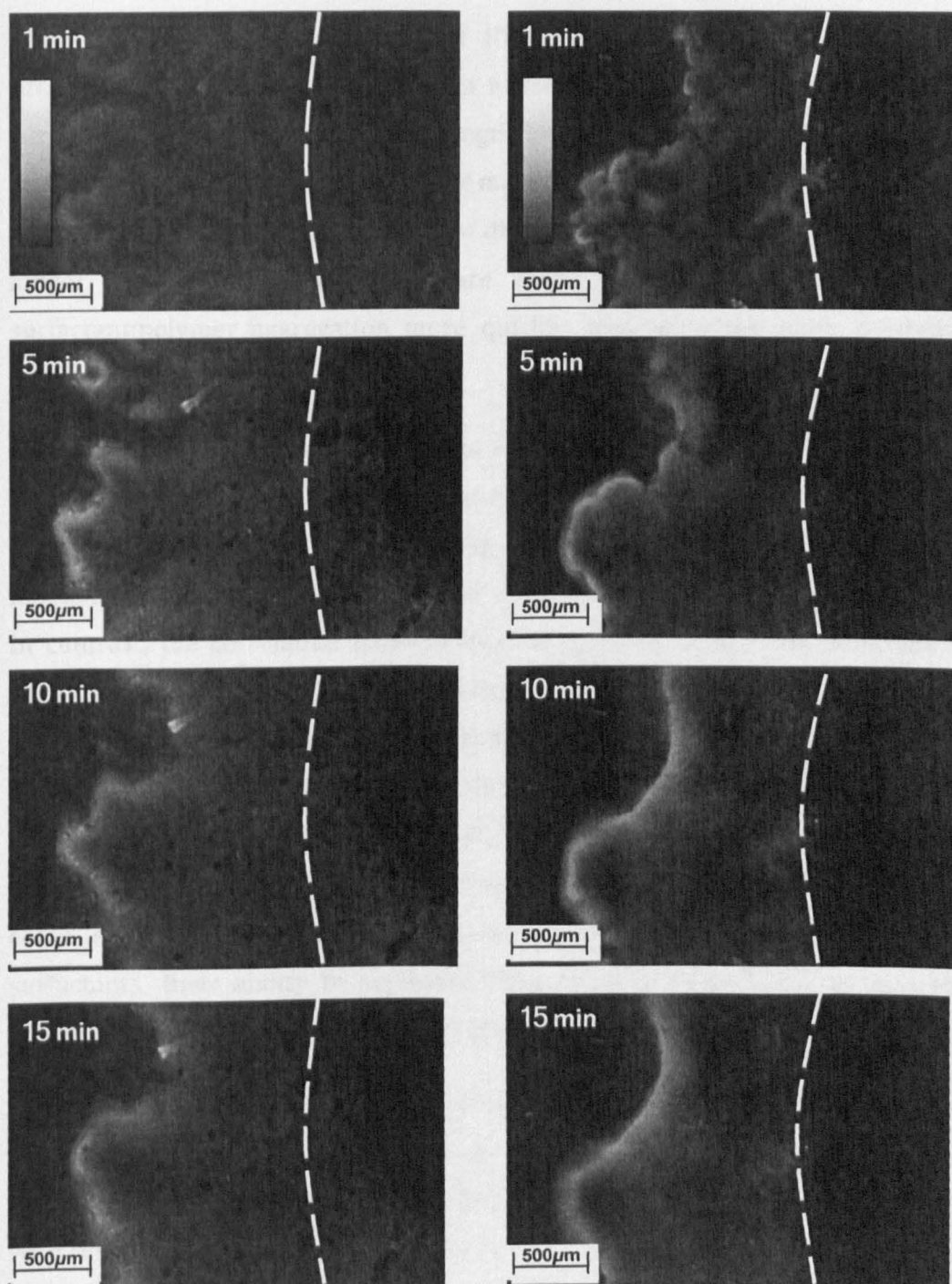


Figure 5.17 Early gel layer formation at the boundary of hydrating HPMC matrices (a) 0%w/w SDS (b) 10%w/w SDS. Matrices contained dextrose as a diluent. Matrix contains 30%HPMC E4M, 10%caffeine anhydrous, (a)no SDS (b)10% SDS, qs dextrose. Confocal fluorescence imaging at Ex 488/Em >510nm. Experiments conducted at $37\pm1^\circ\text{C}$ using water containing 0.008%w/v Congo red as a visualisation aid. Images are coded for fluorescence intensity (highest=white, lowest=black) in accordance with the greyscale bar. Dotted white lines represent the dry matrix boundary at $t=0$ minutes. Scale bar 500µm.

5.5.4 The effect of alkyl chain length of surfactants on HPMC

Table 5.6 shows the dependence of HPMC solution and matrix drug release properties on alkyl chain length of a homologous series of the alkyl sulphate surfactants. Surfactant alkyl chain length had a rank order effect on CAC, SGTT, and also on the drug release kinetics of matrices. The effect of alkyl chain length of surfactants on CAC and SGTT has been discussed previously in Section 5.5.2. The longer chain length surfactants are more hydrophobic and induce the surfactant:polymer aggregation more quickly, leading to the more solubilising effect on HPMC.

The correlation between the ability of surfactants to elevate SGTT (or CPT) of HPMC solutions at the post-micellar phase and their alkyl chain length is exponential increase ($r^2 = 0.9899$) (Figure 5.18). This means the longer chain length of surfactants, the more ability to elevate SGTT or enhance HPMC hydration. In contrast, the correlation between CAC of surfactants in HPMC solutions and their alkyl chain length is exponential decrease ($r^2 = 0.9906$) (Figure 5.19). This means the longer chain length of surfactants, the less concentration required to associate with HPMC. There was a direct correlation ($r = 0.997$) (data not be shown) between the inflexion in the SGTT curve and CAC, and the rate of SGTT elevation at post-micellar concentrations, correlated directly with the carbon chain length of the surfactant. The relationship between different chain length surfactants, their ability to solubilise HPMC and to raise SGTT, reflects their increasing amphiphile nature as carbon chain length is increased.

Figure 5.20 show the effect of alkyl chain length of surfactants on drug release from HPMC matrix tablets containing different diluents. Only the matrices containing dextrose or a mixture of dextrose and MCC (1:1) exhibited an effect with respect to the alkyl chain length of surfactant. In these matrices, longer chain surfactants elicited greater retardation of drug release rate, and in these systems polymer:surfactant interactions may be influencing the diffusion barrier properties of the matrix gel layer. The longer chain length surfactants have more ability to solubilise HPMC, leading to faster gel layer formation. Moreover, if alkyl sulphate surfactants form micelles around methoxyl rich regions of HPMC, the

neutral HPMC is converted into a polyelectrolyte. The negative charges will repel and this will expand the condensed coil of HPMC, leading to an increased viscosity of HPMC solution. This viscous and quickly formed gel layer would be expected to show good retardation of drug release.

Surfactant	Alkyl sulphate chain length	Surfactant concentration (mM) at		*Drug release T80% (min)
		CAC	SGTT	
SHS	6	500	300	167
SOS	8	130	100	162
SDeS	10	30	22	195
SDS	12	4	6	222

Table 5.6 Dependence of HPMC solution and matrix drug release properties on alkylsulphate chain length (Results from Section 5.5.1.1, 5.5.1.3 and 5.5.3.3)

*Matrices contained 10% surfactant and dextrose as diluent

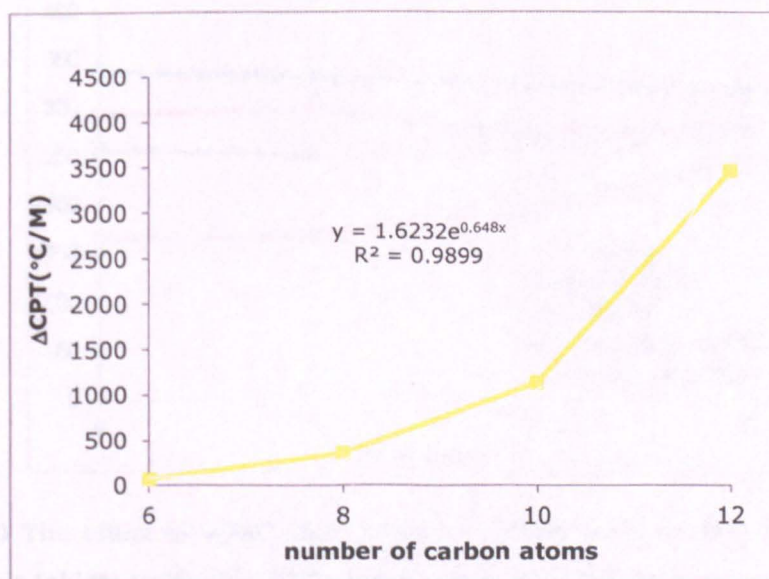


Figure 5.18 The correlation between the ability of surfactants to elevate SGTT of 1%w/w HPMC solution and their alkyl chain length (Results from Section 5.5.1.3)

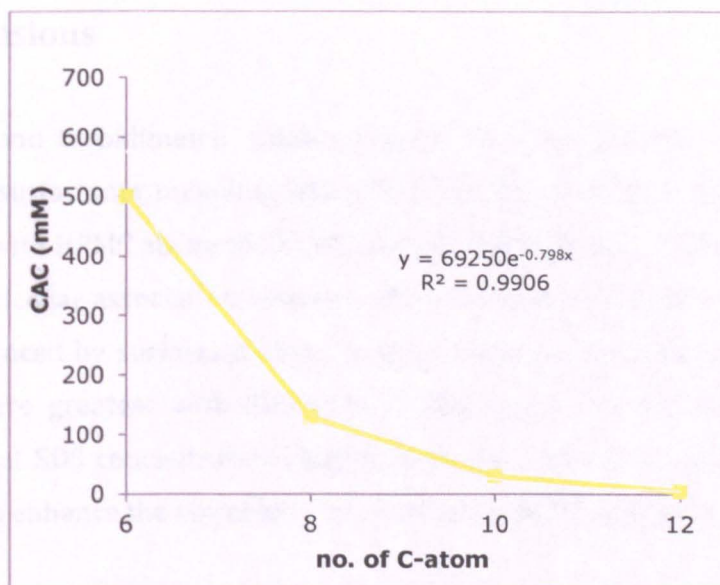


Figure 5.19 The correlation between the CAC of surfactants in a 0.1%w/w HPMC solution and their alkyl chain length (Results from Section 5.5.1.1)

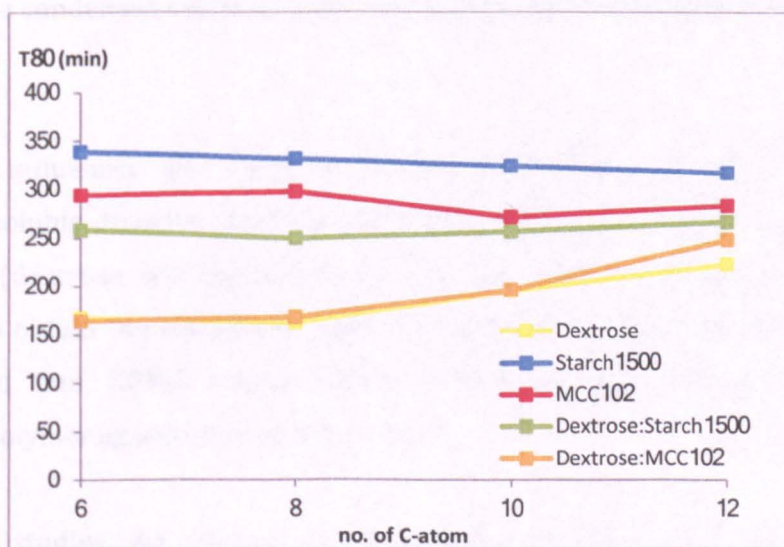


Figure 5.20 The effect of alkyl chain length of surfactants on drug release from HPMC matrix tablets containing different diluents (Results from Section 5.5.3.3)

5.6 Conclusions

Tensiometric and turbidimetric studies suggest that this homologous series of alkyl sulphate surfactants, including SHS (C6), SOS (C8), SDeS (C10), and SDS (C12) can associate with HPMC above their CAC, and solubilise HPMC. These results also suggest that micellar association between alkyl sulphate surfactants and HPMC is strongly influenced by surfactant chain length. Amongst the surfactants studied the effects were greatest with SDS (C12). Rheological studies also provided evidence that at SDS concentrations higher than the CAC the surfactant:polymer interaction can enhance the viscoelastic properties of HPMC solutions .

The interaction between these alkyl sulphate surfactants and HPMC are postulated to be a surfactant:polymer association. The ionic surfactants might form micelle around the methoxyl rich region (hydrophobic area) of HPMC and convert the neutral HPMC into a polyelectrolyte. The negative charge repel can also stretch HPMC from a condensed coil to an extended configuration, leading to more viscous solutions.

Surfactants influenced the extended release performance of HPMC matrices containing soluble diluents (dextrose), insoluble diluents (MCC102), and mixture of diluents (dextrose and MCC102 (1:1)) but not those containing Starch1500. However, to obtain the retardation effect of drug release, the surfactant amount incorporated into HPMC matrix tablets should be high enough to induce surfactant:polymer aggregation in the gel layer.

From these studies, the release retarding effects of SDS suggest it may have application as an ingredient to improve the release performance of HPMC matrices. This will be studied and discussed in the next chapter.

Chapter 6

The Recovery of HPMC matrices using SDS

6.1 Rationale

In the previous study of the effect of alkyl sulphate surfactants on HPMC (Chapter 5), it was postulated that a surfactant:HPMC interaction might influence the diffusion barrier properties of the matrix gel layer by micellar solubilisation of the polymer. At the surfactant content above 10%w/w, sodium dodecyl sulphate (SDS) could retard the drug release from HPMC matrix using dextrose or MCC as diluents. This suggests SDS may be useful in improving the release performance of HPMC matrices in particular cases. In this chapter, SDS will be investigated whether SDS can be used as a 'magic' ingredient to recover HPMC matrices (a) in failing formulations and (b) under challenging conditions.

6.2 Introduction

6.2.1 The previous studies of SDS and HPMC

Combinations of sodium dodecyl sulphate (SDS) with HPMC or other cellulose ethers have been widely studied. Studies of solution interactions between SDS and HPMC showed how SDS can alter the hydrophobic-hydrophilic balance of HPMC through micellar solubilisation of hydrophobic region of the polymer (Nilsson 1995). The addition of SDS was also found to enhance the viscosity of a modified HPMC (Synchron) solutions, and 15%SDS incorporated in matrix tablets elicited a considerable retardation of drug release rate. The proposed mechanism was that

anionic surfactants were able to bind to non-ionic polymers such as HPMC, and to increase the viscosity of the matrix gel layer (Daly et al 1984). In another study increased SDS concentration was found to decrease the release rate of propanolol hydrochloride from HPMC matrices. In this case, SDS, an anionic surfactant was believed to form an ion pair complex with propanolol, a cationic drug (Ford et al 1991b, Nokhodchi et al 2002). A different study showed how the retarding effect of ionic surfactants on matrix drug release was found to depend on the concentration of surfactant molecules and was effective only when both surfactants and the drug were ionised and had opposite charges (Feely & Davis 1988).

Other studies have found conversely, that incorporated surfactants can cause increases in matrix drug release rate (Efentakis et al 1991). The mechanisms postulate were (i) that surfactants reduced the interfacial tension between drug and dissolution fluid, and (ii) surfactants dissolve to form pores which aid the access of dissolution fluid and facilitate the egress of dissolved drug. The surfactant may also reduce interparticle adhesion within HPMC matrix tablets, leading to increases in dissolution rate through enhanced disintegration. Nokhodchi et al (1999) found that SDS increased the release rate of theophylline from HPMC matrices.

It is important to also note that SDS has been used in dissolution media for HPMC matrix tablets which the release rate of the insoluble drugs was increased by the wetting characteristics of SDS (Maggi et al 1996).

6.2.2 Previous studies of the failing HPMC matrix formulations and under challenging conditions

Many additives, tablet diluents and drugs have been found to influence the extended release performance of HPMC matrices. In this section we will briefly review only those which can accelerate the drug release, or in extreme cases, destroy the extended release performance of HPMC matrix tablets. Here is a summary of effects reported in the literature, with their postulated mechanisms:

Highly soluble drugs can act as pore formers, forming micro-cavities and making the gel structure more porous and weaker, hence leading to increased drug release rates (Yang & Fassihi 1997). An increased content of microcrystalline cellulose can, in some cases, change the dissolution profile by accentuating the burst effect. Non-swellable insoluble fillers, for example, 10% dicalcium phosphate can completely destroy sustained release properties of HPMC matrix tablets in low polymer content tablets (Alderman 1984). Likewise, high valency ionic salts can prevent polymer hydration increasing matrix erosion (Pygall et al 2009). In low polymer tablets, a 10% concentration of various ionic salts was found to interfere with gel layer formation, leading to premature dissolution, the effect being proportional to the valency of the salt (Alderman 1984). An increase in ionic strength resulted at first in dissolution rates decreasing to a minimum, before giving rising to a 'burst' release profile (Mitchell et al 1990a). Other dissolved materials in the dissolution media such as glycine, ethanol and dissolved sugars can also adversely influence extended release characteristics. Glycine in dissolution media lead to the increase in the dissolution rate of HPMC matrix tablets. Once glycine concentration reached a critical level between 0.5M and 1.0M the formulation failed and 'dose dumping' was observed (Foster 2004).

Increasing ethanol level in the dissolution media has been found to increase the aspirin release from HPMC matrices. Cloud point studies suggest that ethanol retard polymer hydration (Roberts et al 2007).

A range of dietary sugars have been found to influence the drug release performance of HPMC matrices (Methocel™ K4M CR). They retarded drug release at lower sugar concentrations, but markedly accelerated drug release above a critical sugar concentration (S_{CRIT}). Studies of early gel layer formation suggested that sugars suppress HPMC particle swelling and coalescence of the gel layer, and reducing the diffusion barrier properties of the gel layer (Williams et al 2009).

The effect of a combination of sugar and salts has been investigated by Williams et al (2010b) who found that each solute suppress HPMC hydration, and their effects reflect a rank order of Hofmeister series. However, there was no evidence of synergy or antagonism. In dissolution tests, sodium chloride and trisodium citrate

reduce the S_{CRIT} of sucrose. Williams et al (2010a) have been tried to improve the resistance of HPMC matrices to dissolved sugar by using variable diluents and HPMC grades. They found that matrices containing MCC as the sole diluent provided the extended release for 10 h, and small particle size HPMC (HPMC K100M and K100LV) also improve the sugar resistance.

In Chapter 4, organic salts were also found to influence the drug release performance of HPMC matrices (Methocel™ E4M CR, 63-90 μ m sieved fraction). The small hydrophilic molecules accelerated drug release by removing water from polymer hydration sheath of HPMC, and hence poor gel layer formation or even disintegration. Sodium acetate and disodium succinate showed the potential to destroy the extended release performance of HPMC matrix tablets, and induce the burst release.

6.3 Chapter Aims and Objectives

In this chapter, the ability of SDS as an internally added ingredient to improve or recover the extended release performance of HPMC matrices (i) in failing formulations, and (ii) under challenging conditions are investigated. In particular, the experimental work in this chapter, investigates the effect of SDS on:

- 'Failing formulations': The extended release performance of HPMC matrices containing sodium acetate and disodium succinate, organic salts which were found to accelerate drug release or exhibited burst release for fractionated HPMC E4M matrices (Chapter 4).
- 'Challenging conditions': The extended release performance of HPMC matrices in dissolution medium containing sucrose which was found to suppress matrix gel layer formation and accelerate drug release with high sugar concentration (Williams et al 2009).

6.4 Materials and Methods

6.4.1 HPMC matrix tablet

The composition of the matrix tablets used in this work is shown in Table 6.1 and 6.2. HPMC USP Type 2910 (Methocel™ E4M CR Premium EP/USP) and details of other materials used in the matrices are given in Appendix 1. They were manufactured by the method described in Section 6.4.4.

6.4.2 Failing formulations

Sodium acetate and disodium succinate were selected to incorporate in HPMC matrix tablets as they exhibited the most potential to accelerate drug release or exhibited burst release for fractionated HPMC E4M matrices (Chapter 4). The sources and batch numbers of these materials are documented in Appendix 1. Fractionated HPMC E4M and dextrose were used in the formulation because this combination exhibited the most clearly effect of organic salts on HPMC matrices. This was investigated and discussed in Chapter 4.

6.4.3 Challenging conditions

Dietary sugars have been found to influence the drug release performance of HPMC matrices (Methocel™ K4M) as described previously. Sucrose was selected for its high potential effect. Williams et al (2009) found that the concentration required to $SCRIT$ of sucrose is 0.7M, so in this study a range of sucrose concentrations from 0.2M to 2.0M was used in the dissolution media. Deionized water was used as a control dissolution medium. The source and batch numbers of these materials are documented in Appendix 1.

6.4.4 Manufacture of matrix tablets

Matrix tablets weighing 250 ± 5 mg were manufactured using a Manesty F3 single punch tablet press (Manesty, Liverpool, UK) at a compression pressure of 280MPa,

using 8 mm flat-faced punches (I Holland, Nottingham, UK) as described in section 2.2.6. The formulations of HPMC matrices used in the studies shown in Table 5.1 and 5.2.

Ingredients	Weight Composition (%w/w)		
	A	B	Control
Caffeine anhydrous ^a	10.0	10.0	10.0
HPMC ^b	30.0	30.0	30.0
SDS	10.0	10.0	-
Sodium acetate	10.0	-	-
Disodium succinate	-	10.0	-
Dextrose	40.0	40.0	60.0

Table 6.1 The formulation of HPMC matrix tablets used in the 'failing matrices' studies.

^a <125 μ m sieve fraction. ^b63-90 μ m sieve fraction. Full details of all materials are provided in Appendix 1.

Ingredients	Weight Composition (%w/w)			
	C	D	E	Control
Caffeine anhydrous ^a	10.0	10.0	10.0	10.0
HPMC	30.0	30.0	30.0	30.0
SDS	1.0	5.0	10.0	-
Dextrose	59.0	55.0	50.0	60.0

Table 6.2 The formulation of HPMC matrix tablets used in the 'challenging conditions' studies.

^a <125 μ m sieve fraction. Full details of all materials are provided in Appendix 1.

6.4.5 Dissolution testing

Drug release profiles of HPMC matrices were determined at $37\pm0.5^{\circ}\text{C}$ in 900ml of degassed dissolution media (water for failing formulations studies; water and sucrose solutions for challenging conditions studies) using USP dissolution apparatus I (basket) at 100rpm (Dissolutest, Prolabo, France). Full details of the method are provided in section 2.2.7.

UV detection of caffeine in the presence of sucrose has been studied spectrophotometrically by Williams et al (2009). Increasing sucrose concentration can cause an increase in UV absorbance at 273nm, the wavelength used for caffeine detection. To avoid the interference from sucrose absorbance, sucrose medium (without drug) was used as the blank in each dissolution test to correct for the background absorbance of the sugar. The final determination of the drug concentration at the end of the test was conducted to confirm the 100% release of all matrices.

6.4.6 Photography of hydrating HPMC matrix tablets

The hydrated matrix tablets taken from USP dissolution baskets during the dissolution test were imaged at 0min, 10 min, 1hour, and 8hours using a handheld digital microscope (Celestron LLC, Torrance, CA, USA) and a digital camera (Canon Ixus55, Oita, Japan)

6.5 Results and Discussion

6.5.1 Does SDS enhance the extended release properties of the 'failing formulation'?

Figure 6.1 and 6.2 show the effect of adding 5% and 10%w/w SDS to HPMC matrix tablets containing 10% acetate Na and 10% succinate diNa. These two organic salts the markedly accelerated drug release from fractionated HPMC E4M matrices almost certainly through Hofmeister effects, in which ion rearrangement HPMC and suppressing particle swelling and matrix gel layer formation, leading to the burst release (Cacace et al 1997; Cho et al 2006). Matrices containing either 5% or 10% SDS exhibited burst release, and also released faster than those with acetate. This might because (i) SDS solubilise caffeine so that drug released more quickly, (ii) there was a high content of soluble ingredients in the matrices (~70%w/w including caffeine, dextrose, organic salt and surfactant) which might suppress polymer swelling and gel formation (Bajwa et al 2006), and induce rapid water penetration into the matrix system, possibly through osmotic pressure (Maderuelo et al 2011). As fractionated HPMC E4M is slow hydrated so that the matrices exhibited burst release before the gel layer could be formed.

Some authors found that matrices containing high solubility and high content drugs exhibited high release rate or burst release as the drug may remain at the matrix surface which can release immediately after the matrix tablet exposed to the dissolution medium (Batycky et al 1997; Velasco et al 1999; Huang & Brazel 2001). Carlsson et al (1986; 1988) reported that there was synergistic effect between SDS and NaCl which adding a small amount salt to EHEC:SDS solutions resulted in a first dramatic reduction of the cloud point. However, this occurred at much below the cmc. This might support our study which matrices containing organic salts and SDS exhibited burst release without gel layer formation.

In this case, SDS could not enhance the extended release properties of HPMC E4M matrices containing succinate diNa and acetate Na.

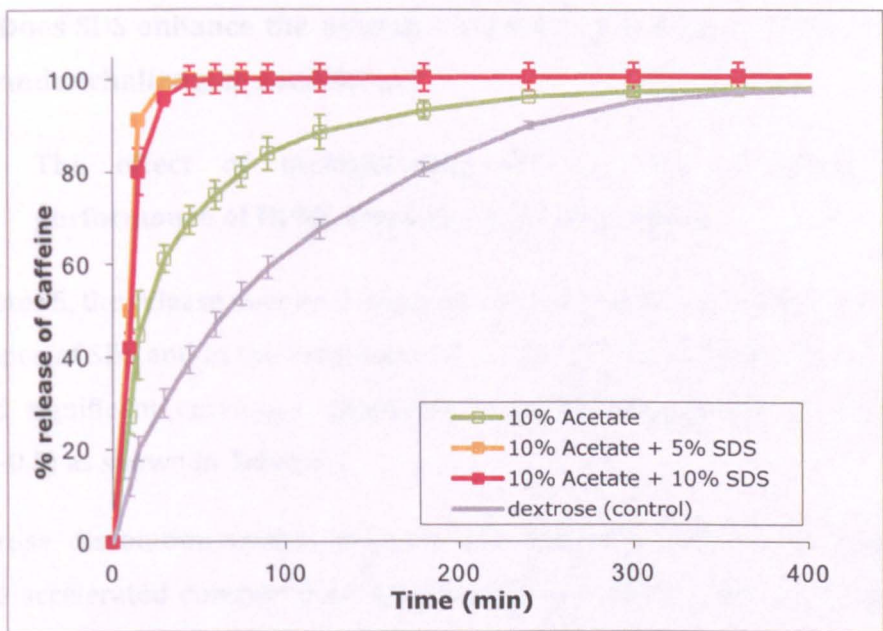


Figure 6.1 ‘Failing formulations’ study: The effect of SDS on the release profile of HPMC matrices containing sodium acetate. USP I , 100rpm, 37°C in water. Matrix composition in Table 6.1. Mean($n=3$) \pm 1S.D.

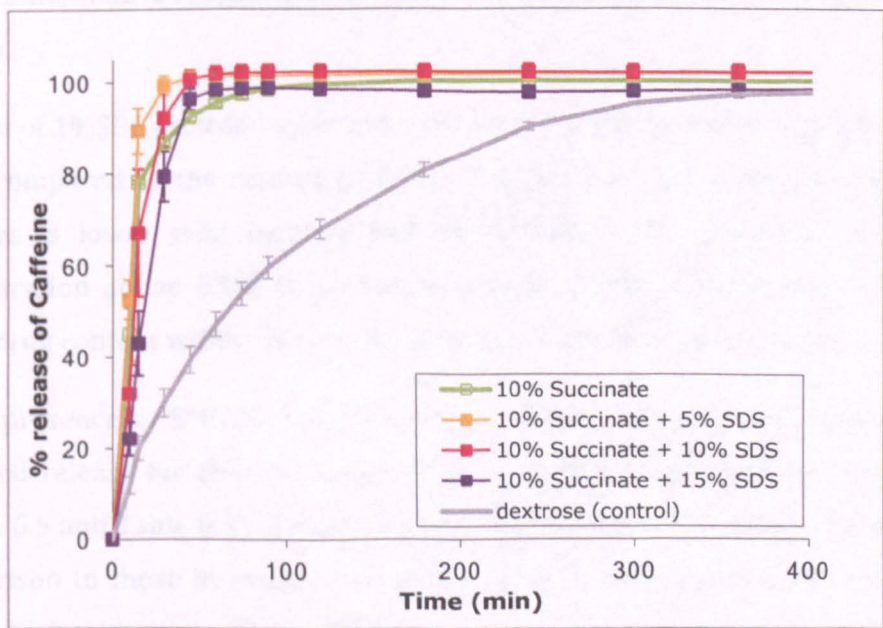


Figure 6.2 ‘Failing formulations’ study: The effect of SDS on the release profile of HPMC matrices containing disodium succinate. USP I , 100rpm, 37°C in water. Matrix composition in Table 6.2. Mean($n=3$) \pm 1S.D.

6.5.2 Does SDS enhance the extended release properties of HPMC matrices under challenging conditions?

6.5.2.1 The effect of incorporating SDS on the extended release performance of HPMC matrices in sucrose media

In Chapter 5, the release over an 8 hour period of the matrices in water was shown in absence of SDS and in the presence of 1, 5 and 10%SDS. These release profiles showed significant curvature suggesting a diffusion-based release mechanism ($n \sim 0.4-0.5$) as shown in Table 6.3.

In sucrose dissolution media, drug release from the matrices excluding SDS became accelerated compared to drug release in water as shown in Figure 6.3. The rate of drug release was in a rank order of sucrose concentration, except in 1.5M and 2.0M sucrose:

$1.0M \sim 0.8M \sim 0.7M \sim 0.6M \sim 0.5M > (1.5M) > 0.4M > (2.0M) > 0.2M > 0M$ (water)

Incorporating SDS into the HPMC matrix tablets could show the capability to improve the matrix release profiles in sucrose media as shown in Figure 6.4, 6.5 and 6.6.

Amount of 1%SDS retarded matrix drug release in 0.2M and 0.4M sucrose medium when compared to the control (0%SDS) (Figure 6.4). Drug release rate (k) of matrices is lower with incorporated SDS (Table 6.3). However, in sucrose concentration above 0.5M these matrix tablets exhibited immediate release of 100% drug content within 30 minutes whether or not SDS was present.

In the presence of 5%SDS, the progressively slower drug release occurred and extended release for over 10 hour period in sucrose concentration up to 0.6M (Figure 6.5 and Table 6.3). Release profiles also exhibited the reduce curvature in comparison to those in water. In sucrose concentration above 0.8M, the matrix tablets both with and without 5%SDS exhibited immediate release of 100% drug content within 1 hour.

Therefore, 1%SDS and 5%SDS can recover the extended release performance of HPMC matrices in sucrose dissolution media up to 0.4M and 0.7M respectively when compare to the control matrix tablets which have no SDS, but when compare to the drug release in water, 1%SDS and 5%SDS can maintain the retardation only in 0.2M sucrose and up to 0.6 sucrose respectively.

Moreover, 10%SDS can recover the extended release performance of HPMC matrices in sucrose dissolution media up to 2.0M when compare to the control matrix tablets which have no SDS (Figure 6.6 and Table 6.3). The progressively slower drug release occurred and extended release for over 15 hour period in sucrose concentration between 0.2M and 1.0M. When compare to the drug release in water, the same effect was found. In sucrose concentration 1.5M, the drug release acceleration was however found until ~3hours and then retardation occurred afterwards which exhibited biphasic dissolution profile. This can be considered as a critical concentration as there may have more factors affecting the drug release from above this concentration. The saturation approach of the dissolution media may be one possibility. The release profile in 2.0M sucrose exhibited the same pattern as in 1.5M sucrose, but there was very small rate of release ($k=1.53$) since the beginning, and hence exhibited extended release over 16 hour.

Interestingly, drug release in 2.0M sucrose exhibited a delayed immediate release profile, but again, there was no difference between a matrix with or without SDS (Figure 6.4 and 6.5). This delayed immediate release might be a result of the decrease of drug solubility in sucrose medium as they exhibited a greater erosional release mechanism ($n\sim 1$) (Figure 6.3). However, with 10% SDS the matrices exhibited progressively retarded release compared with control (Figure 6.6) although there was the great erosional contribution release mechanism either with or without SDS. This might because 10%SDS could enhance the erosion resistance of the gel layer.

Sucrose concentration (M)	0% SDS			1% SDS			5% SDS			10% SDS		
	<i>k</i>	<i>n</i>	<i>r</i> ²	<i>k</i>	<i>n</i>	<i>r</i> ²	<i>k</i>	<i>n</i>	<i>r</i> ²	<i>k</i>	<i>n</i>	<i>r</i> ²
water	6.65	0.477	0.9982	9.73	0.4126	0.9993	8.97	0.430	0.9979	4.02	0.557	0.9978
0.2	15.17	0.342	0.9988	7.75	0.443	0.9994	-	-	-	4.87	0.514	0.9976
0.4	43.77	0.190	1.0000	6.47	0.550	0.9941	8.51	0.405	0.9982	4.30	0.519	0.9984
0.5	(a)	(a)	(a)	(b)	(b)	(b)	-	-	-	-	-	-
0.6	(a)	(a)	(a)	(a)	(a)	(a)	6.45	0.458	0.9983	4.72	0.474	0.9975
0.7	(a)	(a)	(a)	-	-	-	17.49	0.367	0.9995	5.22	0.450	0.9963
0.8	(a)	(a)	(a)	-	-	-	(b)	(b)	(b)	-	-	-
1.0	(a)	(a)	(a)	-	-	-	(b)	(b)	(b)	10.94	0.321	0.9832
1.5	(b)	(b)	(b)	-	-	-	-	-	-	18.93	0.276	0.9589
2.0	3.82	1.337	0.9979	1.00	1.043	0.9958	1.56	1.094	0.9893	1.53	0.845	0.9340

Table 6.3 'Challenging conditions studies: The effect of incorporated SDS into HPMC matrices on drug release kinetics in different sucrose concentration using the modified power law. Fitted up to 80% cumulative release. Modified power law is described by Ford et al (1987). Matrix composition in Table 6.2. *k* is the kinetic constant. *n* is the diffusional exponent. *r*² is determination coefficient.

(a) Drug release >80% within 15 min. (b) Drug release >80% within 30 min.

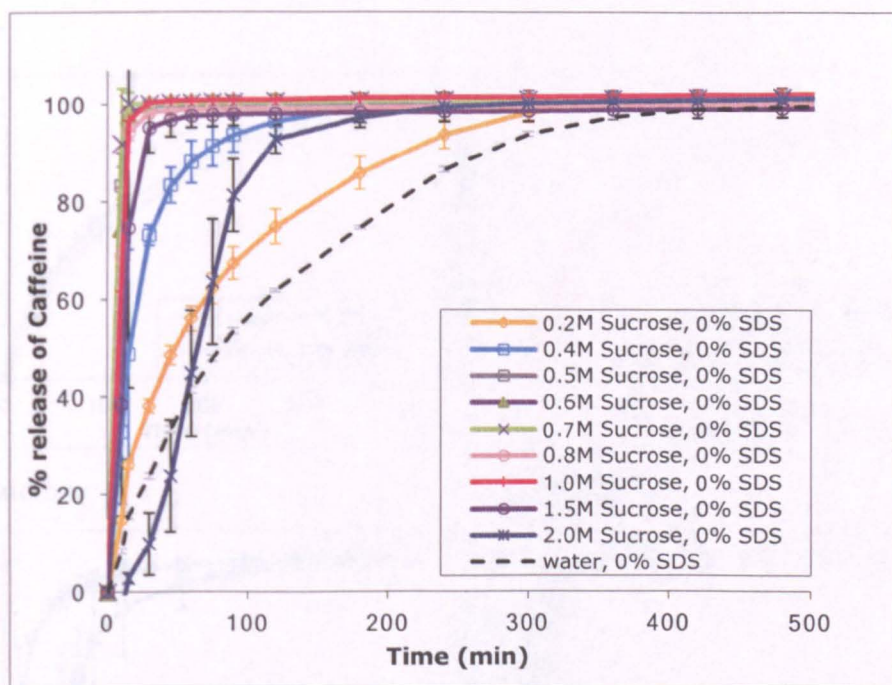
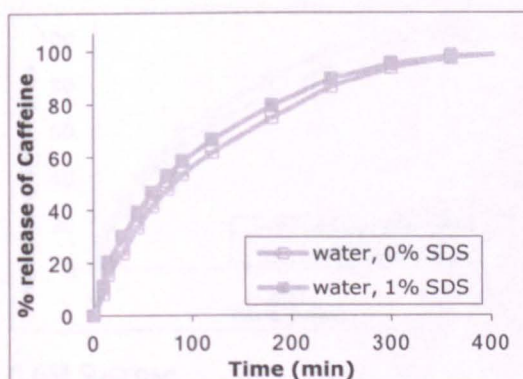
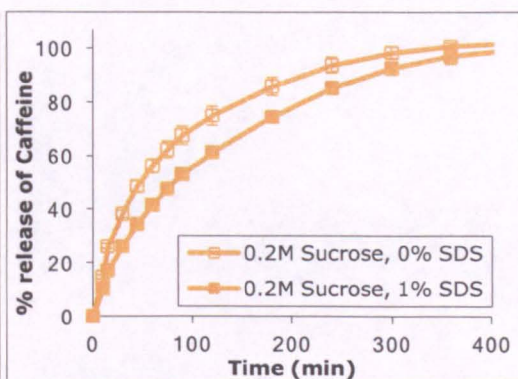


Figure 6.3 'Challenging conditions' study: The drug release performance of HPMC matrices without SDS (control) in a range of sucrose dissolution media. Matrix composition in Table 6.2. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D.

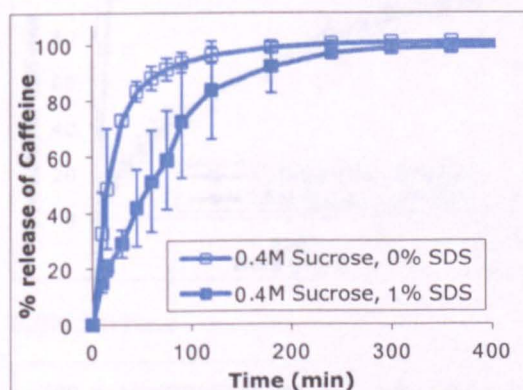
Water



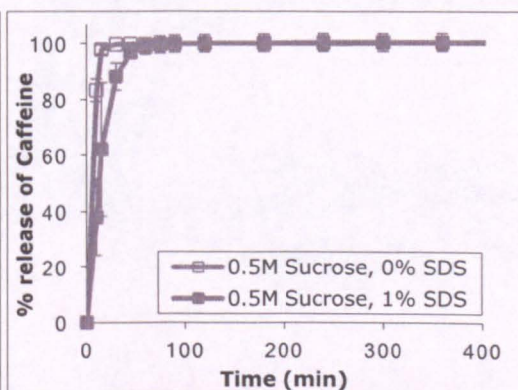
0.2M Sucrose



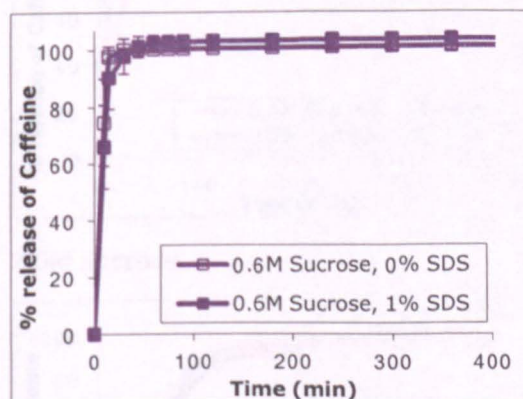
0.4M Sucrose



0.5M Sucrose



0.6M Sucrose



2.0M Sucrose

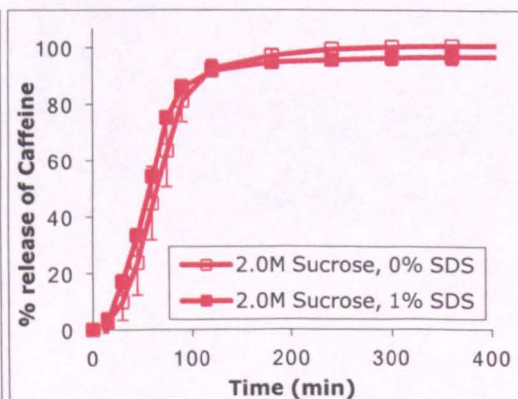


Figure 6.4 'Challenging conditions' study: The effect of incorporating 1%w/w SDS on the drug release profile of HPMC matrices in different sucrose media. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D. Matrix composition in Table 6.2.

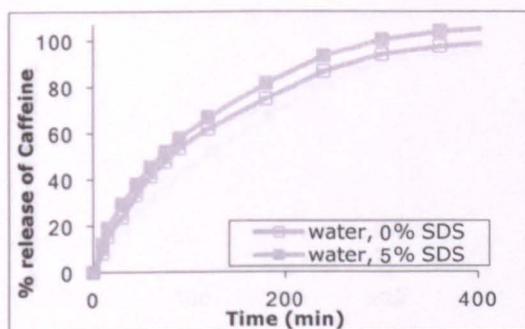
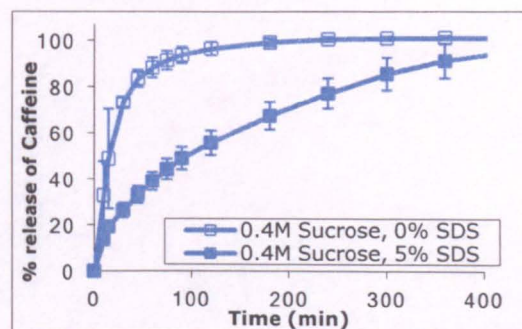
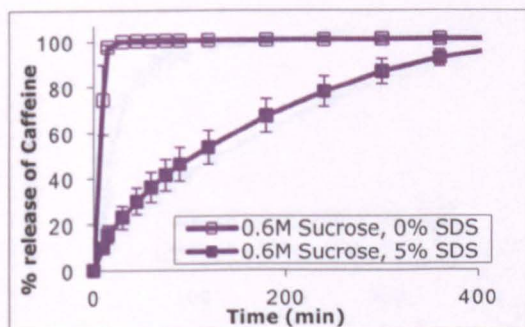
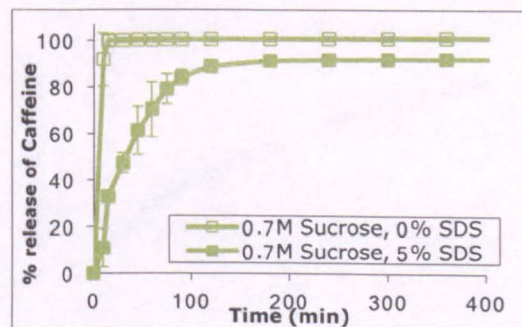
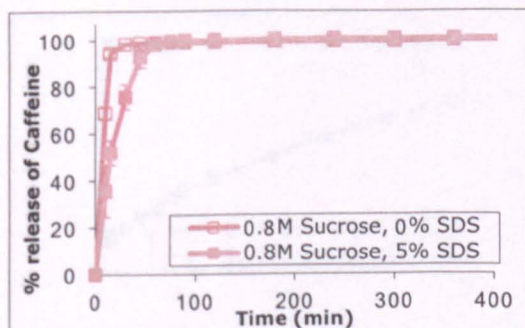
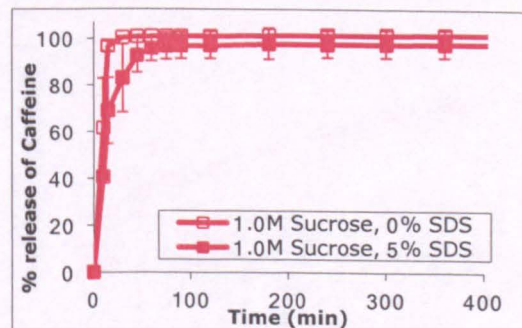
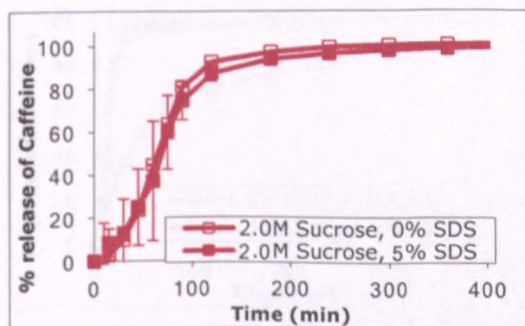
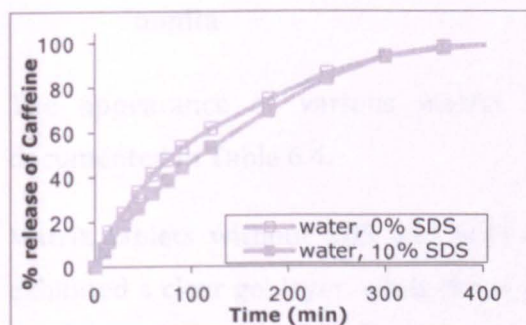
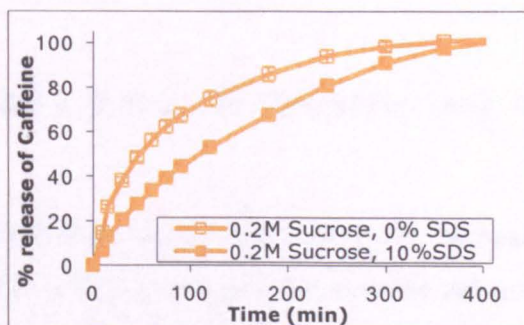
Water**0.4M Sucrose****0.6M Sucrose****0.7M Sucrose****0.8M Sucrose****1.0M Sucrose****2.0M Sucrose**

Figure 6.5 'Challenging conditions' study: The effect of incorporating 5%w/w SDS on the drug release profile of HPMC matrices in different sucrose media. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D. Matrix composition in Table 6.2.

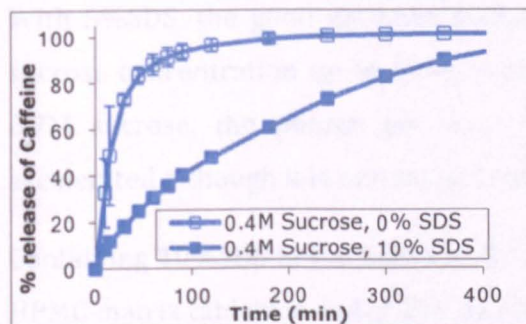
Water



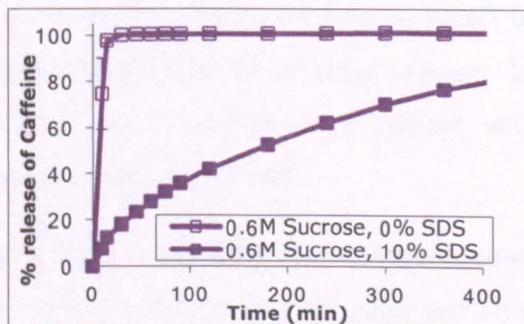
0.2M Sucrose



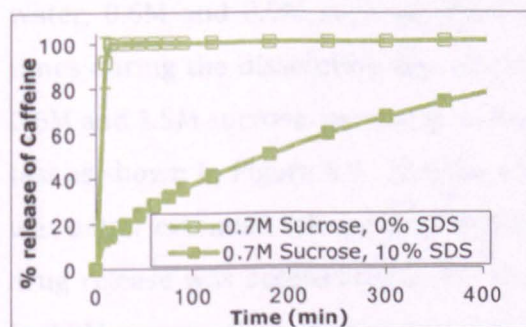
0.4M Sucrose



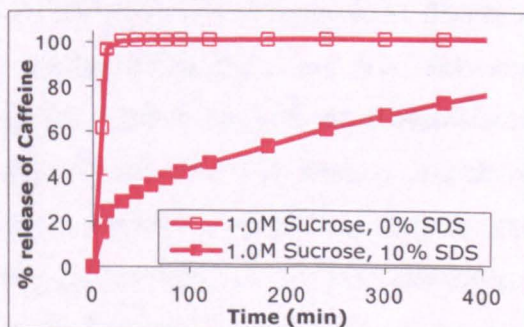
0.6M Sucrose



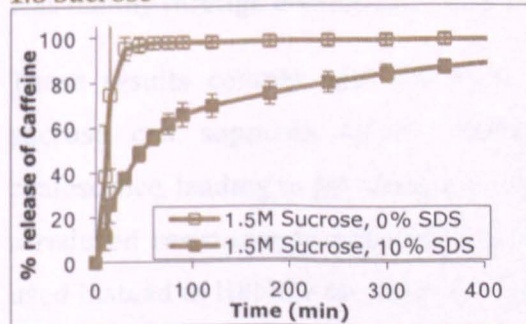
0.7M Sucrose



1.0M Sucrose



1.5 Sucrose



2.0M

Sucrose

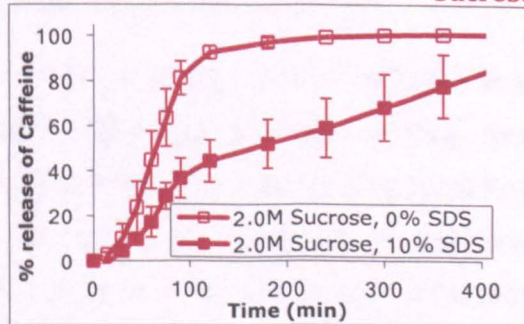


Figure 6.6 'Challenging conditions' study: The effect of incorporating 10%w/w SDS on the drug release profile of HPMC matrices in different sucrose media. USP I, 100rpm, 37°C in water. Mean ($n=3$) \pm 1S.D. Matrix composition in Table 6.2.

6.5.2.2 The effect of SDS on the appearance of HPMC matrices in sucrose media

The appearance of various matrix tablets during the dissolution tests is documented in Table 6.4.

Matrix tablets without SDS and with 1%SDS in water and 0.2M-0.4M sucrose exhibited a clear gel layer, while the matrix tablets in above 0.5M sucrose did not appear to form gel layer at all. This would explain their immediate release profile.

With 5%SDS, the good gel layer formation of HPMC matrix tablets occurred in sucrose concentration up to 0.6M, leading to the retardation of drug release. In 0.7M sucrose, the poorer gel layer was formed, and the drug release was accelerated although it is better than control matrix without SDS.

Containing 10%SDS in the matrices demonstrated the good gel layer formation of HPMC matrix tablets in water and sucrose concentration up to 1.5M, leading to the retardation of drug release. The photographs of the matrix tablets hydrated in water, 0.6M and 2.0M sucrose taken from USP dissolution baskets at different times during the dissolution test are also shown in Figure 6.7 and 6.8. Between 0.6M and 1.5M sucrose, there was a clear gel mass left in the end of the dissolution test as shown in Figure 6.9. In 1.5M sucrose, the gel layer was formed, and there was better extended release performance than control matrix without SDS, but the drug release was accelerated until ~3hours and then became retard afterwards. In 2.0M sucrose, there was no gel layer formation, but the drug release mechanism was mainly through erosion and exhibited the extended release profile.

These results comply with the study of William (2009) who concluded that sucrose can suppress HPMC (Methocel™ K4M CR) particle swelling and coalescence, leading to gel structures with poorer diffusion-barrier properties and a reduced resistance to physical erosion. In the present study, HPMC E4M was used instead of HPMC K4M, and dextrose was used as a diluent instead of lactose. HPMC E4M has a higher level of methoxyl substitution than K4M, and will therefore be more discriminative.

In the lower amount of sucrose, there was less potential to suppress the gel layer formation of HPMC, and hence SDS had chance to form micelles and solubilise HPMC, leading to better gel layer formation. 5%SDS has more potential than 1%SDS to conduct micellar solubilisation with HPMC, and hence 5%SDS provided a better recovery effect in sucrose concentration up to 0.6M.

In the higher amount of sucrose, sucrose had more potential to suppress HPMC particle swelling and coalescence, while 1%SDS and 5%SDS still had less potential to undergo micellar solubilisation with HPMC, the matrices then became accelerated or even immediate release in sucrose concentration above 0.2M and 0.7M respectively.

On the other hand, 10%SDS exhibited high potential to undergo micellar solubilisation with HPMC in a wide range of sucrose concentrations (0.2M-2.0M), leading to better gel layer formation. This suggests that 10%SDS is a good key to recover the extended release performance of HPMC matrices and induce the resistance of the matrix tablets in sucrose media.

Dissolution media	0% SDS matrices	1% SDS matrices	5% SDS matrices	10% SDS matrices
Water	Clear gel layer	Clear gel layer	Clear gel layer	Clear gel layer
0.2M sucrose	Clear gel layer	Clear gel layer	-	Clear gel layer
0.4M sucrose	Clear gel layer, swollen core	Clear gel layer, swollen core	Clear gel layer, clear gel mass left in the end of the test	Clear gel layer
0.5M sucrose	No gel layer, complete erosion in 10 min	Thin clear gel layer, swollen core, depleted in 30 min	-	-
0.6M sucrose	No gel layer, complete erosion in 10 min	No gel layer, complete erosion in 10 min	Clear gel layer, clear gel mass left in the end of the test	Clear gel layer, clear gel mass left in the end of the test
0.7M sucrose	No gel layer, complete erosion in 10 min	-	Clear gel layer, swollen core and eroded	Clear gel layer, clear gel mass left in the end of the test
0.8M sucrose	No gel layer, complete erosion in 10 min	-	Thin clear gel layer, swollen core and eroded	-
1.0M sucrose	No gel layer, complete erosion in 10 min	-	No gel layer, mostly eroded within 30 min	Clear gel layer, clear gel mass (jelly-like) left in the end of the test
1.5M sucrose	No gel layer, mostly eroded within 10 min	-	-	Clear gel layer, small clear gel mass left in the end of the test
2.0M sucrose	Started erosion after 10 min, and depleted by 60 min	Started erosion ~ 10 min	Swollen core, started erosion after 10 min	Tablets floated, started erosion after 30-45 min, no gel left in the end of the test

Table 6.4 'Challenging conditions' study: The observed appearance of HPMC matrix tablets with 0%, 1%, 5%, and 10% SDS during dissolution tests in different sucrose media.

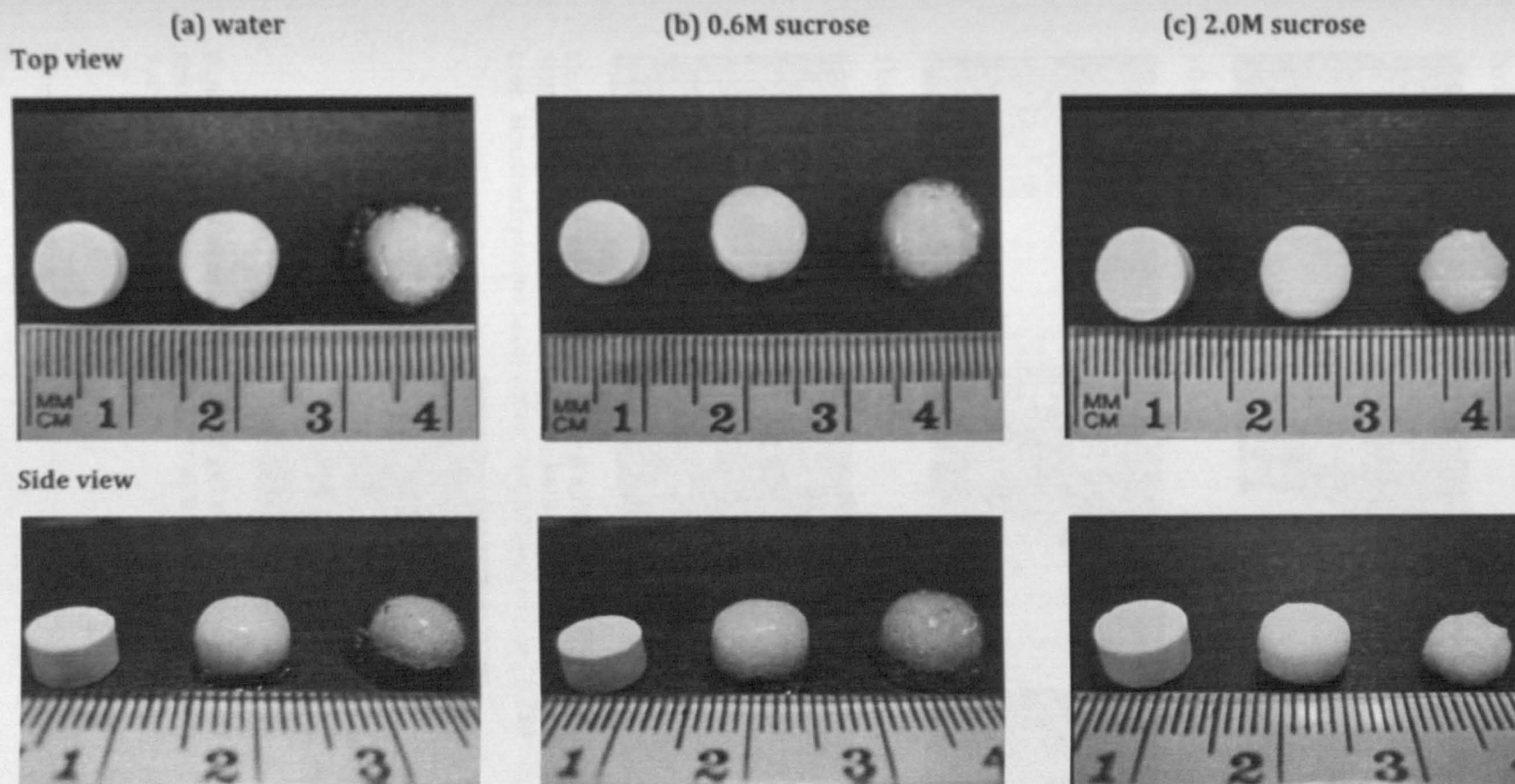


Figure 6.7 'Challenging conditions' study: The photographs of HPMC matrix tablets containing 10% SDS taken from USP dissolution baskets at different times during the dissolution test. Matrices hydrated in (a) water, (b) 0.6M sucrose, or (c) 2.0M sucrose.

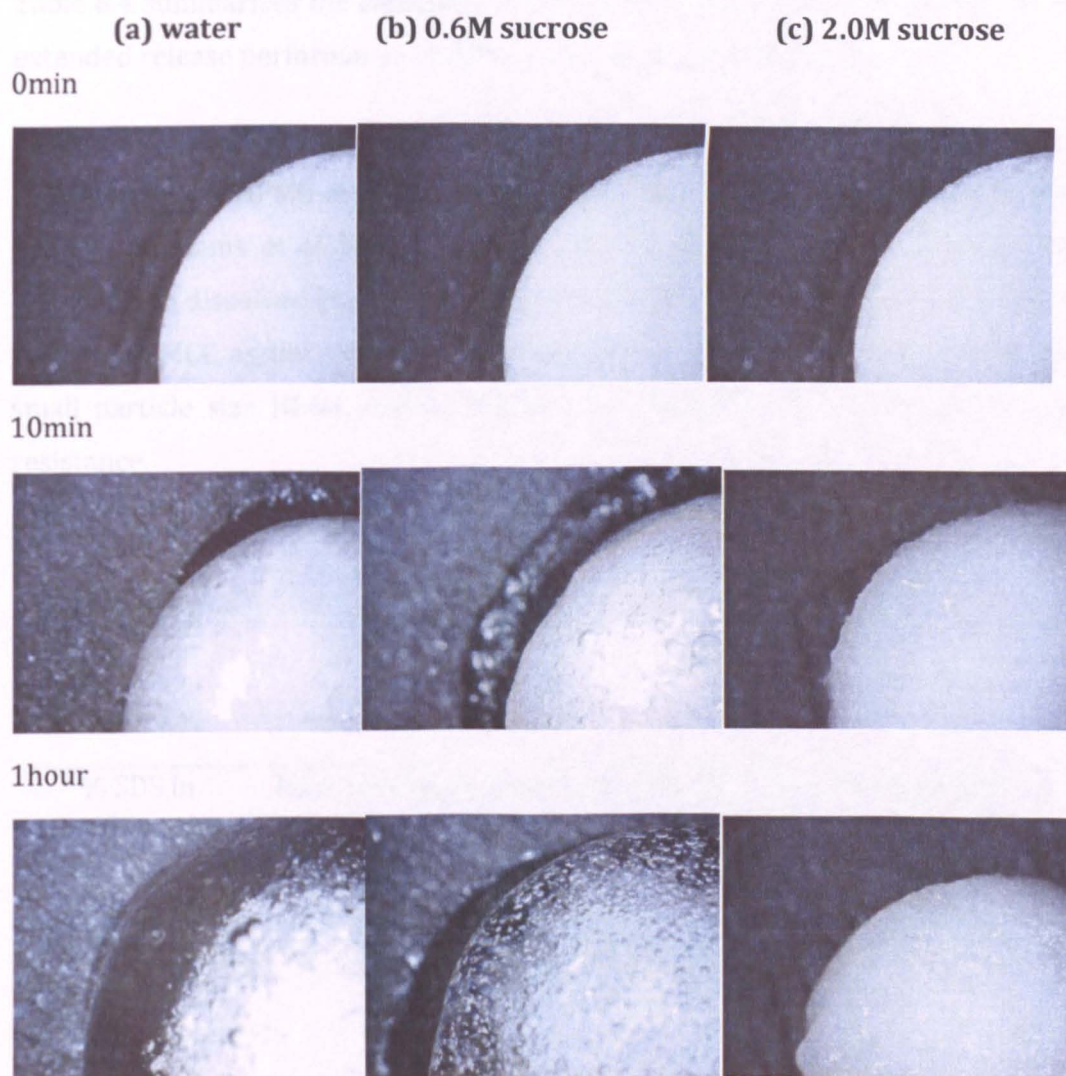


Figure 6.8 The microscopic photographs of HPMC matrix tablets containing 10% SDS taken from USP dissolution baskets at different times during the dissolution test. Matrices hydrated in (a) water, (b) 0.6M sucrose, or (c) 2.0M sucrose



Figure 6.9 The photograph of the gel mass left in the end of the dissolution test taken from USP dissolution baskets at 8 hours. A matrix tablet contains 10%SDS and hydrated in 0.6M sucrose

Table 6.4 summarizes the capability of the different amount of SDS to recover the extended release performance of HPMC matrices in sucrose media.

However, there are other possibilities to enhance the extended release performances of HPMC matrices, for examples, using variable diluents and HPMC grades. Williams et al (2010a) also designed HPMC matrices to improve the resistance to dissolved sugar by using variable diluents. They found that matrices containing MCC as the sole diluent provided the extended release for 10 h, and small particle size HPMC (HPMC K100M and K100LV) also improve the sugar resistance.

% SDS in HPMC matrices	Max. concentration of sucrose media which SDS can recover (M)	
	When compare to the release in water	When compare to control tablets (without SDS)
1	0.2	0.4
5	0.6	0.7
10	2.0	2.0

Table 6.5 'Challenging conditions' study: The capacity of SDS to recover HPMC matrices (with Dextrose as a diluent) in sucrose dissolution media. Matrix composition in Table 6.2. USP I , 100rpm, 37°C in water. Mean (n=3)± 1S.D. Dissolution media: distilled water; sucrose solution (a range of 0.2M-2.0M)

6.6 Conclusions

In the 'failing formulations' studies, SDS could not recover or improve the extended release performance of HPMC matrices. This might because there were too high content of soluble ingredients in matrices which might suppress polymer swelling and gel layer formation, leading to the rapid water penetration and the burst release before gel layer formation. However, SDS may be useful in the formulations containing less soluble substances or different diluents. The further study needs to be conducted.

In the 'challenging conditions' studies, 1%SDS exhibited the low potential to recover the extended release performance of HPMC matrices in sucrose media, while 5%SDS provided more potential and useful to recover the extended release of HPMC matrices in sucrose concentration up to 0.7M. 10%SDS is the best for using to recover the extended release performance of HPMC matrices in sucrose media as it could retard the matrix drug release in sucrose concentration up to 2.0M. However, the high dose of SDS is not suitable for oral administration. The normal level of incorporation of SDS is 0.5-2.5% for oral preparations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. The further studies of using different diluents are interested. The usage of other surfactants will also be useful.

Chapter 7

Overall Discussion and Conclusions

7.1 Overall discussion

7.1.1 Organic salts

This study has revealed the impact of organic salts used as drug counter-ions on HPMC solutions and matrices. Within the limited range of salts studied, the effects on HPMC solution properties (Chapter 3) and HPMC matrix release performance (Chapter 4) appear to be dependent on their molecular structure. They can be categorised both by their effects, and the proposed mechanisms, into 3 groups :

(i) Organic salts with 1-4 C-atoms

These salts (e.g. acetate Na, propionate Na, butyrate Na) depressed the sol-gel transition temperature (SGTT) of HPMC solutions, but had little effect on the polymer surface activity. They accelerated matrix drug release, in comparison with a control matrix in which dextrose was substituted for the salt.. The mechanism of interaction with HPMC is proposed to be that these small hydrophilic molecules act as kosmotropic ions in the Hofmeister series. They compete for, and remove water from the polymer hydration sheath due to their strong water interactions (Alderman 1984; Cacace et al 1997; Cho et al 2006; López-León et al 2007; Yang 2009). This leads to an enhanced tendency for methoxyl-rich regions of the HPMC chain to associate, in accordance with the model of Haque and Morris (1993). The consequence is a lowering of SGTT or precipitation of HPMC by 'salting out'. In matrices, this mechanism would lead to inhibition of particle swelling, a slowing of the rate of polymer hydration and of matrix gel layer formation.

Divalent salts (e.g. fumarate diNa, maleate diNa, succinate diNa, tartrate diNa, malate diNa) exhibit a greater ability to depress SGTT and accelerate matrix drug release. This suggests they have a greater ability to potentiate methoxyl aggregation and phase separation because divalent salts are more highly charged, and further up the Hofmeister series. This is supported by previous studies of the effects of multivalent ions such as phosphate and citrate (Mitchell et al 1991; Kujawinski 2000; Liu et al 2008; Pygall et al 2009).

(ii) Organic salts with 5-8 C-atoms

Aliphatic organic salts containing 5-8 C-atoms elevated the SGTT, reduced the surface tension of HPMC solutions, and retarded matrix drug release in comparison with a control matrix. It has been reported previously that octanoate Na is able to form micelles with a low aggregation number and at a relatively high critical micellar concentration ($\text{cmc} \sim 0.4\text{M}$) (Zemb et al 1983; Kuhn et al 2002; Ruso et al 2004). These longer-chain salts might act as 'salting in' agents, as chaotropic ions in the Hofmeister series (Alderman 1984; Cacace et al 1997; Cho et al 2006; López-León et al 2007). They would enhance the hydration of HPMC through micellar solubilisation of methoxyl-rich regions of the polymer chain, changing the water structure around these hydrophobic regions into regions where water is interacting more extensively with the charged polar groups of the micelle. This interaction would therefore promote polymer affinity for water during HPMC particle swelling, leading to more rapid gel layer formation in HPMC matrices so that matrices containing these salts, would exhibit better extended release properties.

The model of salting out and salting in behaviour on HPMC in solution has been described in previous studies of ionic solutes (Mitchell et al 1990a, Mitchell et al 1991), amino acids (Richardson et al 2006) inorganic salts (Alderman 1984; Bajwa 2006; Liu et al 2008) sugars (Williams 2009) and drugs such as ibuprofen (Ridell et al 1999)

A homologous series of aliphatic organic salts influenced solution and matrix properties in a rank order of hydrocarbon chain length. The increased chain

length corresponds to the more hydrophobicity. This can be implied that their ability to alter HPMC hydration depends on their hydrophobicity. This supports the study of amino acid which found that the effect on SGTT showed the strongest relationship with amino acid hydrophobicity (Richardson et al 2006).

(iii) Organic salts containing an aromatic species

The aromatic organic salts studied (benzoate Na, besilate Na and salicylate Na) all elevated SGTT, enhanced the viscoelastic behaviour of HPMC solutions, but exhibited no influence on polymer surface activity. In this study, matrices containing 60%w/w aromatic salts exhibited retarded release with respect to the control whereas those containing 10%w/w salts generally did not (only 10%w/w besilate could retard drug release).

Aromatic compounds commonly self-associate in water to form stacking rings through π - π interactions (Balasubramanian et al 1989; Sindkhedkar et al 2000; Waters 2002; Sasaki et al 2006; Desai & Parikh 2009; Hao et al 2012). In our study, the aromatic salts are amphiphiles in which their aromatic stacking rings provide the hydrophobic part, and the carboxylic or sulfonic groups, the hydrophilic part. These aromatic compounds (known as hydrotropes) can induce π -stacking aggregation, a configuration that can considerably enhance the aqueous solubility of organic substances if present at a sufficient concentration (Matero 2002). Many studies have used these hydrotropes to solubilise poorly water-soluble drugs (Prakash et al 2009; Jayakumar et al 2010; Kim et al 2010; Shete et al 2010).

Our hypothesis is therefore that aromatic organic salts interact directly with HPMC (as a result of their amphipathic characteristics) through π -stacking aggregation, thereby solubilising hydrophobic sites on the polymer. This might be the reason why these aromatic salts elevated the SGTT. (The paper by Richardson et al (2006) showed the same effects with aromatic amino acids.) However, the amount of these salts must be high enough to allow molecular aggregation and enhance HPMC hydration (Matero 2002). This is perhaps why 10%w/w salts did not retard drug release from HPMC matrices whereas 60%w/w did. Moreover,

because the properties of these aromatic stacks depend on the ring substituents, and besilate has better self-assembly through intermolecular π - π and sulphur-sulphur interactions, this may explain why only this salt could retard drug release at 10%w/w. The hydrophobic regions become negatively charged as a result of solubilisation and absorption of the aromatic salts onto the polymer. These regions of negative charge would repel each other, straightening and extending the polymer chain, making the solution more viscous, and gel-like entanglements more frequent. This would explain the observed rise in G' and G'' .

Touitou & Donbrow (1982b) found that salicylate Na and benzoate Na raised SGT_T of HPMC solutions which they explained that these ions are adsorbed onto the macromolecule and increase the polymer hydration with their carrying water molecules.

7.1.2 Alkyl sulphate surfactants

A homologous series of alkyl sulphate surfactants, including SHS (C6), SOS (C8), SDeS (C10), and SDS (C12), all elevated SGT_T and reduced the surface tension of HPMC solutions. The interaction between these alkyl sulphate surfactants and HPMC are postulated to be surfactant:polymer association. Tensiometric, turbidimetric and rheological studies suggested that these alkyl sulphate surfactants associate with HPMC at concentrations above their critical aggregation concentration (CAC), and they may solubilise HPMC through micellar solubilisation. The results also suggested that micellar association between alkyl sulphate surfactants and HPMC was strongly influenced by surfactant chain length. Amongst the surfactants studied, the effects were greatest with SDS (C12). Avranas & Iliou (2003) also found that the chain length of anionic surfactant influences polymer adsorption at an interface.

There is evidence that ionic surfactants form micelles around hydrophobic methoxyl-rich regions of HPMC (Nilsson 1995). This would convert the neutral

HPMC into a polyelectrolyte. The acquired negative charges would repel, and this would stretch HPMC from a condensed coil to an extended configuration, leading to more viscous solutions (Kulicke & Clasen 2004). With sufficient negative charges, the molecule might behave like NaCMC which is highly resistant to dehydration (Doelker 1993). Dou and Colby (2004) have studied how charge density impacts the rheology of polyelectrolyte solutions. They found that neutral polymers have the lowest viscosity and shortest relaxation time, and weakly charged polyelectrolytes have the highest viscosity and longest relaxation time. The behaviour of more highly-charged polyelectrolytes lies between these limits. This evidence suggests that a low density of charged regions such as would happen with adsorption of SDS, might considerably alter the polymer behaviour and viscosity of HPMC in the gel layer.

HPMC matrices containing small amounts of surfactants were found to accelerate drug release (this was also found by Cao et al (2005)). Turbidimetric studies indicated that these surfactants could solubilise HPMC at post-micellar concentrations and it could be implied that SDS would only improve the extended release performance of HPMC matrices when there is enough concentration to form micelles. This postulate is supported by the study by Silva et al (2011) which suggested the influence of surfactant on HPMC hydrogels occurs in three separate phases depending on the surfactant concentration.

Nokhodchi et al (1999) found that theophylline release from HPMC matrices was accelerated by incorporated SDS because of a changing contribution from erosion. However, there have been many more reports that SDS can retard drug release, when incorporated into HPMC matrices. The mechanisms suggested have been (i) an (unspecified) binding of anionic surfactant to the non-ionic polymer (Daly et al 1984) (ii) ionic interactions between the oppositely charged drug and surfactant which leads to the formation of a low solubility complex (Feely & Davis 1988; Ford et al 1991b; Nokhodchi et al 2002). In our current study, caffeine the model drug, is neutral and therefore ionic interactions between drug and surfactant cannot occur. The effect therefore appears to be related to an influence of the surfactant on the polymer.

Overall, these studies suggest that SDS may be a useful additive with which to improve the extended release performance of and HPMC matrix. In chapter 6, the effect of incorporating SDS into 'problem' HPMC matrices was investigated (i) in formulations that barely sustained release and (ii) matrices failing under challenging dissolution conditions. In these experiments matrices containing HPMC E4M and succinate diNa and acetate Na were used. These formulations exhibit burst release, possibly because the content of soluble ingredients (caffeine, dextrose, organic salt and surfactant) is very high ~70%w/w. Many authors have reported that matrix formulations containing a high content of solubles release a considerable amount of drug immediately after the matrix tablet is exposed to the dissolution medium (Batycky et al 1997; Velasco et al 1999; Huang & Brazel 2001; Maderuelo et al 2011). In this study, SDS could not improve the extended release performance of HPMC matrices containing acetate and succinate.

To provide challenging dissolution conditions, the matrices were exposed to high concentrations of sucrose. A previous study had showed how, at concentrations >0.7M, sucrose accelerates HPMC matrix drug release, by suppressing HPMC hydration., leading to poorer gel layer integrity and reduced resistance to erosion (Williams et al 2009).

In our studies, 1%w/w SDS in HPMC matrices did not help extended release and whilst 5%w/w SDS showed potential, 10%w/w SDS was required to provide a significant improvement. When 10% SDS was incorporated matrices that would have failed in 0.7M sucrose, showed extended release in sucrose concentrations up to 2.0M. Unfortunately this amount of SDS is not suitable for oral administration because although 10%w/w SDS in a 250mg HPMC tablet is only 25mg/tablet, far below the human lethal oral dose (0.5-5 g/kg), the normal usage of SDS in oral preparations is 0.5-2.5%, and higher doses can have laxative effects

Williams et al (2010a) have designed HPMC matrices with improved resistance to dissolved sugar without the use of SDS. They varied the diluent and HPMC grade, and found that matrices containing MCC as the sole diluent, a small particle size of HPMC and a very high viscosity grade (HPMC K100M) improved sucrose resistance up to ~1M.

7.2 Overall conclusions

The studies in this thesis reveal how organic salts incorporated into HPMC matrices influence drug release in a rank order that corresponds to their modulation of the polymer hydration sheath in solution.

A homologous series of aliphatic acid sodium salts influenced solution and matrix properties in rank order of hydrocarbon chain length. Monovalent salts containing 1 to 4 C atoms had little effect on polymer surface activity but depressed sol:gel transition temperatures (SGTT) and accelerated matrix drug release compared with a dextrose control. Divalent salts were more potent, corresponding with other studies of multivalent anions (Kujawinski 2000; Pygall et al 2009). These salts appear to exert Hofmeister effects in which kosmotropic anions compete for available water and dehydrate the polymer hydration sheath, leading to 'salting out' of the polymer (Touitou & Donbrow 1982b; Cacace et al 1997; Cho et al 2006). In matrices this action has been shown to suppress particle swelling and matrix gel layer formation (Pygall et al 2009; Williams et al 2009). Organic monovalent salts from 5 to 8 C atoms increasingly influenced polymer surface activity, elevated SGTT values, and retarded matrix drug release in comparison with a dextrose control. This suggests these salts enhance HPMC hydration, possibly through interaction with hydrophobic regions (Nilsson 1995). It suggests that the ability of the charged ion to destabilise the polymer hydration sheath is opposed, with increasing chain length, by the ability of the hydrophobic chain to interact with and enhance polymer molecular hydration. The effects on matrix drug release also show that the presence of these ions impacts on the water:polymer interactions which would be important to the formation and diffusion barrier properties of the gel layer. In the case of monovalent salts, drug release showed a significant linear correlation with ΔCPT ($r=0.938$, $p<0.01$), where ΔCPT reflects the ability of the anion to disrupt or enhance polymer hydration and is a function of ionization and hydrophobicity, which oppositely affect polymer hydration sheath stability (Richardson et al 2006). In the case of divalent anions, these proved more potent in depressing CPT, and all salts investigated accelerated drug release reflecting similar effects seen with other multivalent inorganic salts (Alderman 1984).

These findings provide guidance for the future formulation of HPMC matrix tablets. For example, high dose drugs with a strongly hydrophilic organic counter-ions should be avoided, and hydrophobic or amphipathic salts might be better to maintain, modulate or even improve extended release properties.

The studies then moved to a series of alkyl sulphate surfactants. The effects of SDS and its homologous series on the sol:gel transition temperature (SGTT) and the surface tension of HPMC solution can be divided into pre-micellar and post-micellar concentration effects. At pre-micellar concentrations these surfactants depressed SGTT in a similar way to monovalent carboxylic acids. Above the critical aggregation concentration (CAC) however, these surfactants decreased the interfacial tension between HPMC and water probably by forming micelles around the hydrophobic regions of HPMC, and hence they elevated SGTT. As mentioned above, these surfactants improve HPMC molecular hydration at post-micellar concentrations, and these effects suggested that SDS might be able to improve the extended release performance of HPMC matrices when there is sufficient SDS in the matrix to form micelles.

Subsequent studies showed that by incorporating 10%w/w SDS, it allowed HPMC matrices that would have otherwise failed in 0.7M sucrose to tolerate concentrations up to 2.0M. This result suggests surfactants may be worth further investigation as extended release co-adjuvants to HPMC in hydrophilic matrix tablets.

7.3 Future work

The following future work would support the studies presented in this thesis, and would also progress our understanding of how organic salts and surfactants influence HPMC properties and matrix release performance:

- The investigation of the impact of these organic salts on the early gel layer formation on HPMC matrices by confocal laser scanning microscopy (CLSM). This would provide more profound understanding of their impact on gel layer formation.
- Studies of gel strength by rheology and texture analysis. This would provide additional insights into the physical consequences of the interactions on gel layer resistance to erosion.
- An investigation of counter-ions in combination with drugs for which they are used as salts.
- An investigation of early gel layer formation, gel strength and release properties in SDS media used for dissolution testing.
- The use of SDS to further improve other formulations or performance under other challenging conditions.
- A study of longer chain-length alkyl sulphates and other pharmaceutical surfactants. Some surfactants will be better tolerated physiologically, require to be present in smaller amounts or may show interesting results in improving the matrix gel layer and the release performance of HPMC matrices.

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Appendix 1

Materials

Material	Brand name/grade	Manufacturer	Batch No
Caffeine anhydrous	Analytical grade	Sigma-Aldrich, Dorset, UK	1308874
HPMC	Methocel™E4M CR	Colorcon Ltd, Dartford,	QF11012N03
	Premium	Kent, UK	TD09012N11
	Methocel™K4M CR		
	Premium		
Organic salts			
Sodium formate	Analytical grade	Sigma-Aldrich, Dorset, UK	00702KC
Sodium acetate, anhydrous	Analytical grade	Alfa aesar	10116203
Sodium propionate	Analytical grade	Sigma-Aldrich, Dorset, UK	035K0039
Sodium butyrate	Analytical grade	Alfa aesar	10120013
Sodium pentanoate	Analytical grade	Merck	S00089 620
Sodium hexanoate	Analytical grade	Sigma/ Fluka	362265/1
Sodium octanoate	Analytical grade	Sigma-Aldrich, Dorset, UK	123K0205
Sodium mesilate	Analytical grade	Sigma-Aldrich, Dorset, UK	06002EB-286
Diodium fumarate	Analytical grade	Alfa aesar	10129838
Sodium hydrogen fumarate	Analytical grade	Alfa aesar	10099719
Disodium tartrate	Analytical grade	Alfa aesar	D7342A
Sodium salicylate	Analytical grade	Sigma-Aldrich, Dorset, UK	1301292
			50107034
Disodium succinate	Analytical grade	Sigma-Aldrich, Dorset, UK	00615CA-176
Sodium benzoate	Analytical grade	Alfa aesar	10115540
Sodium besilate	Analytical grade	Sigma-Aldrich, Dorset, UK	1164882
			31807231
Disodium oxalate	Analytical grade	Alfa aesar	A1897A
Disodium malate, monohydrate	Analytical grade	Fisher/ Acros organics	A0241923
Disodium maleate	Analytical grade	Sigma-Aldrich, Dorset, UK	A0241924
Sodium hexyl sulphate	Analytical grade	Acros organics	A0205516
Sodium octyl sulphate	Analytical grade	Alfa aesar	10144221
Sodium decyl sulphate	Analytical grade	Acros organics	A0273453
Sodium dodecyl sulphate	Reagent plus	Sigma-Aldrich, Dorset, UK	046K0085
	≥98.5%		

Material	Brand name/grade	Manufacturer	Batch No
Tablet diluents			
Dextrose monohydrate	Meritab®	Tate and Lyle, Aahst, Belgium	053733538
Lactose monohydrate	Fast-flo	Foremost Farms, Baraboo, USA	DL00008709
Microcrystalline cellulose	Avicel PH102		7G29497
Magnesium stearate	Technical grade	Sigma-Aldrich, Dorset, UK	
Partially pregelatinized starch	Starch 1500®	Colorcon Ltd, Dartford, Kent, UK	DT200778
Dissolution media			
Sodium chloride	Analytical grade	Fisher scientific, Leicestershire, UK	0737716
Sucrose	Analytical grade	Fisher scientific, Leicestershire, UK	0954097
Deionized water		USF, Elga, Buckinghamshire, UK	
CLSM			
Congo red		Sigma-Aldrich, Dorset, UK	126H2510
Sigmacote®		Sigma-Aldrich, Dorset, UK	103K4360
Water	Maxima HPLC grade (maximum conductance 18.2 MΩ.cm)	USF, Elga, Buckinghamshire, UK	-

Appendix 2

The moisture content of the principal HPMC batch monitored over the duration of work in this thesis

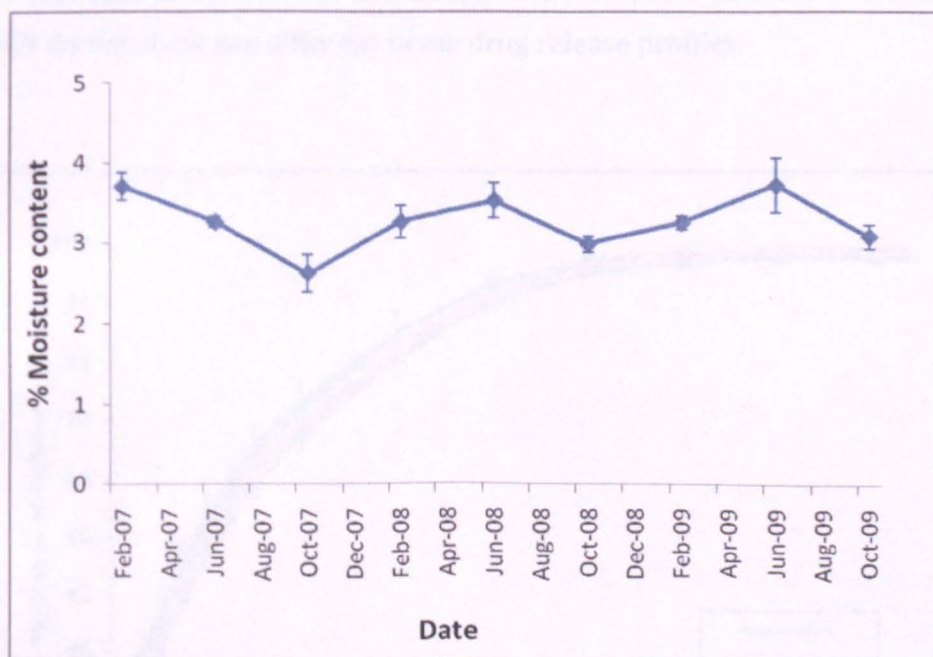


Figure A1 The percentage (% w/w) moisture content of the Methocel™ E4M CR premium (Batch number) used in this study with respect to storage time.

Measurements were made every ~4 months. Mean ($N=3$) \pm 1 s.d.

Appendix 3

The effect of compression force on HPMC matrices using dextrose as a diluent

HPMC matrices using dextrose as a diluent with compression force in the range of 4-16KN do not show any different in the drug release profiles.

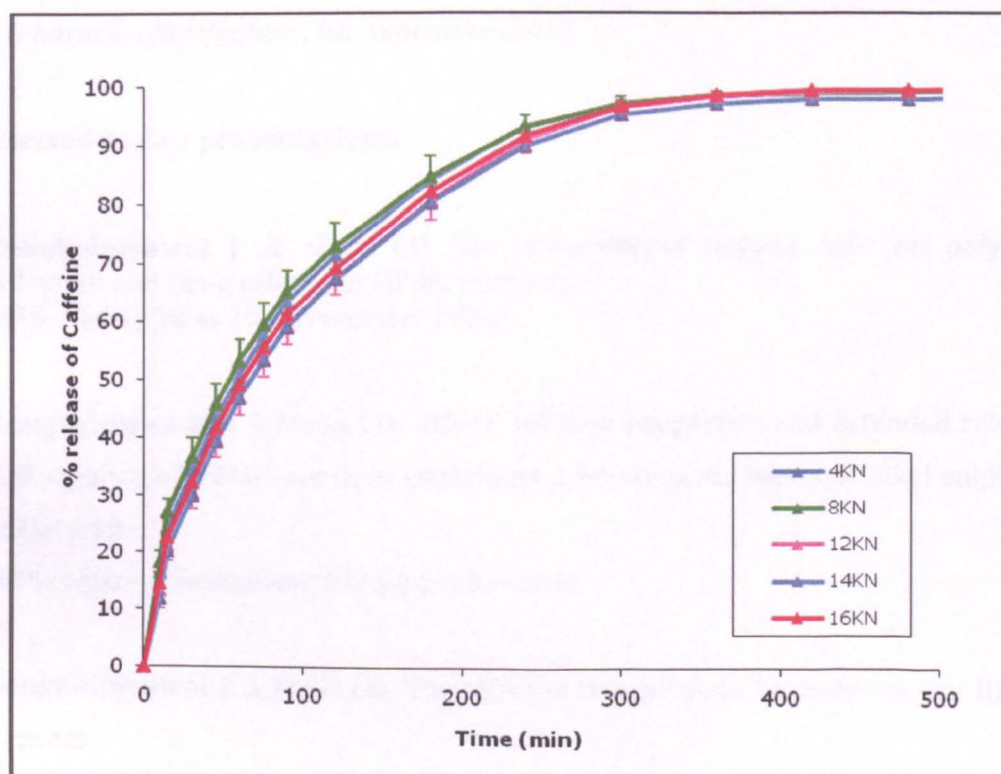


Figure A2 The effect of compression force on the dissolution profile of HPMC matrices using dextrose as a diluent. 8mm, 250mg matrices contain 30%HPMC, 10%caffeine anhydrous, qs diluents. USP I, 100rpm, 37°C in water. Mean (n=3) \pm 1S.D.

Appendix 4

Presentations

The work presented herein has given rise to the following presentations:

Oral presentations:

Mongkolpiyawat J. & Melia CD. HPMC solution properties and extended release performance of HPMC matrices containing a homologous series of alkyl sulphate surfactants.

UKPharmSci, Nottingham, UK, September 2010.

Selected poster presentations:

Mongkolpiyawat J. & Melia CD. The Influence of organic ions on polymer hydration and Drug release in HPMC matrices
AAPS, New Orleans, USA, November 2010.

Mongkolpiyawat J. & Melia CD. HPMC solution properties and extended release performance of HPMC matrices containing a homologous series of alkyl sulphate surfactants.

UKPhramSci , Nottingham, UK, September 2010.

Mongkolpiyawat J. & Melia CD. The Effect of Organic Acid Counter-ions on HPMC Matrices

BPC, Manchester, UK, September 2008.